Henry C. Su (SBN 211202; suh@howrey.com)
Katharine L. Altemus (SBN 227080; altemusk@howrey.com)
HOWREY LLP
1950 University Avenue, 4th Floor
East Palo Alto, California 94303
Telephone: (650) 798-3500
Facsimile: (650) 798-3600

Robert Ruyak
Matthew Wolf
Marc Cohn
HOWREY LLP
1229 Pennsylvania Avenue, NW
Washington, DC 20004
Telephone: (202) 783-0800
Facsimile: (202) 383-6610

Attorneys for Plaintiff
HOLOGIC, INC., CYTYC CORPORATION and HOLOGIC LP

UNITED STATES DISTRICT COURT

NORTHERN DISTRICT OF CALIFORNIA

SAN JOSE DIVISION

HOLOGIC, INC., CYTYC CORPORATION, and HOLOGIC LP,

Plaintiff,

vs.

SENORX, INC.,

Defendant.

AND RELATED COUNTERCLAIMS.

Case No. C08 00133 RMW

AMENDED COMPLAINT FOR PATENT INFRINGEMENT, LANHAM ACT VIOLATIONS, AND STATE UNFAIR COMPETITION SEEKING DAMAGES AND INJUNCTIVE RELIEF

DEMAND FOR JURY TRIAL

Plaintiffs Hologic, Inc., Cytyc Corporation, and Hologic L.P. (together, "Hologic"), by their attorneys, complain against SenoRx, Inc. ("SenoRx"), and allege as follows:

NATURE OF THE ACTION

1. Hologic brings this action to seek damages and injunctive relief arising out of the infringement by SenoRx of U.S. Patent Nos. 5,913,813, 6,413,204, and 6,482,142 (together, the "Patents-In-Suit," attached hereto at Exhibits A, B, and C, respectively), and for related acts of false advertising.

2. Plaintiff Hologic, Inc. is a Delaware corporation with a place of business at 35 Crosby Drive, Bedford, Massachusetts 01730.

3. Plaintiff Cytyc Corporation is a Delaware corporation with a place of business at 250 Campus Drive, Marlborough, Massachusetts 01752.

4. Plaintiff Hologic L.P. is a limited partnership with a place of business at 250 Campus Drive, Marlborough, Massachusetts 01752.

5. Defendant SenoRx is a Delaware corporation with a principal place of business at 11 Columbia, Aliso Viejo, California 92656.

JURISDICTION AND VENUE

6. This Court has subject matter jurisdiction over Hologic's claims of patent infringement and false advertising pursuant to 28 U.S.C. §§ 1331 and 1338(a) because the claims arise under the Patent Act, 35 U.S.C. § 281 and the Lanham Act, 15 U.S.C. § 1125(a), respectively. In addition, this Court has supplemental jurisdiction over the non-Federal claims for relief pursuant to 28 U.S.C. § 1367(a).

7. This Court has personal jurisdiction over SenoRx because, on information and belief, SenoRx regularly and systematically transacts business in this District.

8. Venue is proper in this District pursuant to 28 U.S.C. §§ 1391(b), 1391(c) and 1400(b) because on information and belief, SenoRx has committed, and intends to commit, acts of infringement and false advertising in this District.

\\

INTRADISTRICT ASSIGNMENT

9. This is an Intellectual Property Action within the meaning of the Court's Assignment Plan, and therefore is subject to assignment on a district-wide basis pursuant to Civil Local Rule 3-2(b).

BACKGROUND

10. Hologic is a leading developer, manufacturer and supplier of premium diagnostic, therapeutic and medical imaging systems dedicated to serving the healthcare needs of women, and a leading developer of state-of-the-art digital imaging technology for general radiography and mammography applications. Hologic's business units are focused on mammography and breast biopsy, direct-to-digital x-ray for general radiography applications, treatment of breast cancer, cervical cancer screening gynecological surgery, osteoporosis assessment, and mini C-arm imaging for orthopedic applications. Each year, more than one million women are diagnosed with breast cancer, while hundreds of thousands of them fall victim to this dreaded disease. Hologic has achieved a leading market position in breast cancer detection in the United States.

11. Through its recently-acquired Cytyc subsidiary, Hologic has, *inter alia*, developed and marketed innovative radiation delivery systems for the treatment of cancer since 1995. One such system is the MammoSite® Radiation Therapy System, which delivers targeted, therapeutically effective doses of radiation directly to the breast tissue where cancer is most likely to recur. To effect this delivery of radiation, the MammoSite® System provides for the placement of a radiation source inside the human body, specifically within a cavity created in the breast tissue after the cancerous tumor has been removed.

12. The MammoSite® Radiation Therapy System has been widely used by radiation oncologists and breast surgeons to treat breast cancer patients who are undergoing breast conservation therapy. Breast conservation therapy involves excising only the cancerous tumor in a surgical procedure known as a lumpectomy and preserving the healthy breast tissue, including the nipple, the skin, the fatty tissue underneath and the pectoral muscle. Because this operation does not remove the entire breast (as is the case with a total mastectomy), there is a chance that some pre-cancerous and/or

cancerous cells remain at the margins of excision and therefore the cancer may return. Accordingly, it is recommended that patients undergo certain post-operative treatments such as chemotherapy and radiation therapy to eliminate or minimize the likelihood that the cancer will recur.

13. The term brachytherapy refers to radiation therapy in which the radiation source is placed in proximity to the tissue being treated and contrasts with the use of an external radiation source, which irradiates a wider area of the body that includes the tissue to be treated. Because it places the radiation source within the cavity created by the lumpectomy, in proximity to the tissue that surrounded the cancerous tumor, the MammoSite® Radiation Therapy System provides a treatment method referred to as breast brachytherapy. The placement of the radiation source at the lumpectomy site is achieved through the use of a balloon catheter applicator.

14. In May 2002, Proxima Therapeutics, Inc. ("Proxima Therapeutics") obtained clearance from the U.S. Food and Drug Administration ("FDA") to market the MammoSite® Radiation Therapy System as a new medical device.

15. Proxima Therapeutics was a pioneer in breast radiation therapy and made significant investments in the research, development and testing of therapeutically effective devices and methods for implementing breast brachytherapy, including the MammoSite® system.

16. To protect those investments, Proxima Therapeutics applied for and obtained a number of patents, including U.S. Patent Nos. 5,913,813, 6,413,204, and 6,482,142, which are the subject of this Complaint.

17. In 2005, Proxima Therapeutics was acquired by Cytyc Corporation, and, in 2007, Hologic, Inc. combined with Cytyc Corporation. Cytyc Corporation is the assignee and owner of U.S. Patent Nos. 5,913,813, 6,413,204, and 6,482,142, which are the subject of this Complaint.

18. Hologic continues to invest significant time, money, and other resources to improving and refining the MammoSite® Radiation Therapy System.

19. On information and belief, SenoRx submitted a premarket notification under Section 510(k) of the Food, Drug and Cosmetic Act to the FDA for its device for implementing breast brachytherapy, to be marketed under the name SenoRad Multi-Lumen Balloon Source Applicator For

Brachytherapy (the "SENORAD MULTI-LUMEN BALLOON"). As required by Section 510(k), SenoRx had to persuade the FDA that its device is a substantial equivalent to an already approved and classified medical device.

20. The FDA approved SenoRx's premarket notification on or about May 18, 2007, as evidenced by the Section 510(k) summary (No. K071229), a true and correct copy of which is attached as Exhibit D. The FDA determined that there is substantial equivalence between SenoRx's SENORAD MULTI-LUMEN BALLOON and Hologic's patented MammoSite® Radiation Therapy System. The notification states: "The SenoRad applicator has the following similarities to the previously cleared predicate devices: same indications for use; same intended use; same intended treatment site; ***same operating principle; same technological characteristics; equivalent dosimetric characteristics***; and same sterilization method. The materials of construction vary in a manner that has no impact on device safety. In summary, the SenoRad Multi-Lumen Balloon Source Applicator as described in this submission is substantially equivalent to the predicate devices." (*See* Exhibit D (emphasis added).)

21. In accordance with Proxima's FDA clearance, the MammoSite® Instruction Manual, under the heading Contraindications, cautions "Do not deliver radiation if the minimum distance from the balloon surface to the skin surface is less than 5 mm; or if the distance from the balloon surface to the skin surface is 5 mm over a continuous length greater than 1 cm on the surface of the skin." A true and correct copy of the MammoSite Instruction Manual is attached as Exhibit E.

22. In accordance with Proxima's FDA clearance, the MammoSite® Instruction Manual warns users that "[i]maging should verify a minimum distance of 5 mm from balloon surface to skin surface; however, a minimum distance of 7 mm from balloon surface to skin surface is recommended." *See* Exhibit E.

23. On information and belief, in accordance with SenoRx's FDA approval, the Instructions for Use for the SenoRx device warns users "[d]o not use if a skin surface to balloon surface distance of less than 5mm will result." A true and correct copy of the Instructions For Use for the SenoRx Multi-Lumen Balloon Source Applicator For Brachytherapy is attached as Exhibit F.

24. On information and belief, SenoRx has given the SenoRad device the commercial moniker the "Contura™ Multi-Lumen Balloon."

COUNT ONE – INFRINGEMENT OF U.S. PATENT NO. 5,913,813

25. Hologic incorporates by reference its allegations in Paragraphs 1-24 above.

26. On information and belief, and based on likely evidentiary support after a reasonable opportunity for further investigation or discovery, SenoRx is presently making, using, offering for sale, and/or selling a device for implementing brachytherapy (including, without limitation, the Contura™ Multi-Lumen Balloon) that infringes one or more claims of U.S. Patent No. 5,913,813 (the "'813 patent"), literally or under the doctrine of equivalents in violation of one or more subsections of 35 U.S.C. § 271. A true and correct copy of the '813 patent is attached as Exhibit A.

27. On information and belief, and based on likely evidentiary support after a reasonable opportunity for further investigation or discovery, SenoRx is presently inducing or contributing to the infringement of one or more claims of the '813 patent.

28. On information and belief, SenoRx's infringement of the '813 patent has been willful and wanton because SenoRx has had notice of the '813 patent.

29. If SenoRx's infringing activities are not preliminarily and permanently enjoined, Hologic will suffer irreparable harm that cannot be adequately compensated by a monetary award.

30. Hologic has suffered economic harm as a result of SenoRx's infringing activities in an amount to be proven at trial.

COUNT TWO – INFRINGEMENT OF U.S. PATENT NO. 6,413,204

31. Hologic incorporates by reference its allegations in Paragraphs 1-30 above.

32. On information and belief, and based on likely evidentiary support after a reasonable opportunity for further investigation or discovery, SenoRx is presently making, using, offering for sale, selling a device for implementing brachytherapy (including, without limitation, the Contura™ Multi-Lumen Balloon) that infringes one or more claims of U.S. Patent No. 6,413,204 (the "'204 patent"), literally or under the doctrine of equivalents in violation of one or more subsections of 35 U.S.C. § 271. A true and correct copy of the '204 patent is attached as Exhibit B.

33. On information and belief, and based on likely evidentiary support after a reasonable opportunity for further investigation or discovery, SenoRx is presently inducing or contributing to the infringement of one or more claims of the '204 patent.

34. On information and belief, SenoRx's infringement of the '204 patent has been willful and wanton because SenoRx has had notice of the '204 patent.

35. If SenoRx's infringing activities are not preliminarily and permanently enjoined, Hologic will suffer irreparable harm that cannot be adequately compensated by a monetary award.

36. Hologic has suffered economic harm as a result of SenoRx's infringing activities in an amount to be proven at trial.

COUNT THREE – INFRINGEMENT OF U.S. PATENT NO. 6,482,142

37. Hologic incorporates by reference its allegations in Paragraphs 1-36 above.

38. On information and belief, and based on likely evidentiary support after a reasonable opportunity for further investigation or discovery, SenoRx is presently making, using, offering for sale, selling a device for implementing brachytherapy (including, without limitation, the Contura™ Multi-Lumen Balloon) that infringes one or more claims of U.S. Patent No. 6,482,142 (the "'142 patent"), literally or under the doctrine of equivalents in violation of one or more subsections of 35 U.S.C. § 271. A true and correct copy of the '142 patent is attached as Exhibit C.

39. On information and belief, and based on likely evidentiary support after a reasonable opportunity for further investigation or discovery, SenoRx is presently inducing or contributing to the infringement of one or more claims of the '142 patent.

40. On information and belief, SenoRx's infringement of the '142 patent has been willful and wanton because SenoRx has had notice of the '142 patent.

41. If SenoRx's infringing activities are not preliminarily and permanently enjoined, Hologic will suffer irreparable harm that cannot be adequately compensated by a monetary award.

42. Hologic has suffered economic harm as a result of SenoRx's infringing activities in an amount to be proven at trial.

\\

COUNT FOUR – FEDERAL UNFAIR COMPETITION
(LANHAM ACT § 43(A); 15 U.S.C. § 1125(a))

43. Hologic incorporates by reference its allegations in Paragraphs 1-42 above.

44. On information and belief, and based on likely evidentiary support after a reasonable opportunity for further investigation or discovery, SenoRx has and is currently advertising its Contura™ Multi-Lumen Balloon in interstate commerce through customer presentations which compare the MammoSite® Applicator and the Contura™ Multi-Lumen Balloon. A true and correct copy of one such SenoRx customer presentation is attached as Exhibit G.

45. On information and belief, and based on likely evidentiary support after a reasonable opportunity for further investigation or discovery, SenoRx through its customer presentations cites purportedly scientifically reliable data to advertise that the Contura™ Multi-Lumen Balloon is superior to the MammoSite® Applicator. SenoRx advertises, for example, that the Contura™ Multi-Lumen Balloon is superior to the MammoSite® Applicator radiation treatment of surgical margins in close proximity to (at, for example, less than 5 mm from) the surface of the skin. (*See* Exhibit G).

46. On information and belief, and based on likely evidentiary support after a reasonable opportunity for further investigation or discovery, such SenoRx's customer presentations are false, misleading, and likely to deceive the public in that SenoRx is advertising the capabilities of the Contura™ Multi-Lumen Balloon for which SenoRx has not received FDA clearance or approval. SenoRx, for example, has no brachytherapy device which is FDA cleared or approved for treatment of superficial excision margins in close proximity to the surface of the skin.

47. On information and belief, and based on likely evidentiary support after a reasonable opportunity for further investigation or discovery, SenoRx's customer presentations are false, misleading, and likely to deceive the public as a result of SenoRx's failure to disclose one or more material facts, as for example, the material fact that the FDA cleared labeling for both the predicate MammoSite® device and the Contura™ Multi-Lumen Balloon explicitly warns against specific use with a balloon surface-to-skin surface distance of less than 5 mm.

\\

48. SenoRx's false and misleading representations have confused and misled, and will continue to confuse and mislead, a substantial number of persons who receive these misleading representations into believing those representations, such as, for example, that the Contura™ Multi-Lumen Balloon is FDA cleared and/or approved for administration of radiation treatment to superficial resection cavities near the surface of the skin.

49. On information and belief, and based on likely evidentiary support after a reasonable opportunity for further investigation or discovery, SenoRx has made, used, approved, and sponsored these misleading representations in promotional materials that disparage and/or discredit Hologic's MammoSite® Applicator, and misrepresent the comparative superiority of SenoRx's Contura™ Multi-Lumen Balloon.

50. On information and belief, and based on likely evidentiary support after a reasonable opportunity for further investigation or discovery, SenoRx relies on these misleading representations to encourage customers to purchase the Contura™ Multi-Lumen Balloon by suggesting that the Contura™ device treats a patient base (as for example, those patients with superficial excision cavities close to the skin surface) for whom treatment with the MammoSite® Applicator is contraindicated.

51. On information and belief, and based on likely evidentiary support after a reasonable opportunity for further investigation or discovery, SenoRx continues to make such misleading representations with the specific intent that these representations deceive and mislead consumers and potential consumers of brachytherapy products with the result that, *inter alia*, they will purchase Contura™ Multi-Lumen Balloons when they would otherwise have purchased MammoSite® Applicators.

52. On information and belief, and based on likely evidentiary support after a reasonable opportunity for further investigation or discovery, SenoRx's misleading statements have been placed in interstate commerce, have actually deceived consumers and the public, create a likelihood that a substantial segment of consumers and the public will be deceived, have substantially damaged Hologic, and violate 15 U.S.C. § 1125(a).

\\

53. By reason of SenoRx's acts alleged herein, Hologic has suffered, and will continue to suffer, damage to its business, reputation, and good will. This harm constitutes an injury for which Hologic has no adequate remedy at law.

54. If SenoRx's false and misleading advertisements are not preliminarily and permanently enjoined, Hologic will suffer irreparable harm that cannot be adequately compensated by a monetary award.

55. Hologic has suffered economic harm as a result of SenoRx's false and misleading advertisement in an amount to be proven at trial.

COUNT FIVE – STATE UNFAIR COMPETITION
(CAL. BUS. & PROF. CODE SECTION 17200 *et seq.*)

56. Hologic incorporates by reference its allegations in Paragraphs 1-55 above.

57. SenoRx's unlawful, unfair, and/or fraudulent business acts and practices described herein constitute unfair competition in violation of Section 17200, *et seq*. of the California Business and Professions Code.

58. On information and belief, and based on likely evidentiary support after a reasonable opportunity for further investigation or discovery, SenoRx has and is currently advertising its Contura™ Multi-Lumen Balloon through customer presentations which compare the MammoSite® Applicator and the Contura™ Multi-Lumen Balloon. *See* Exhibit G.

59. On information and belief, and based on likely evidentiary support after a reasonable opportunity for further investigation or discovery, SenoRx through its customer presentations cites purportedly scientifically reliable data to advertise that the Contura™ Multi-Lumen Balloon is superior to the MammoSite® Applicator. SenoRx advertises, for example, that the Contura™ Multi-Lumen Balloon is superior to the MammoSite® Applicator radiation treatment of surgical margins in close proximity to (at, for example, less than 5 mm from) the surface of the skin. (*See* Exhibit G).

60. On information and belief, and based on likely evidentiary support after a reasonable opportunity for further investigation or discovery, such SenoRx's customer presentations are false, misleading, and likely to deceive the public in that SenoRx is advertising capabilities of the Contura™

Multi-Lumen Balloon for which SenoRx has not received FDA clearance or approval. SenoRx, for example, has no brachytherapy device which is FDA cleared or approved for treatment of superficial excision margins in close proximity to the surface of the skin.

61. On information and belief, and based on likely evidentiary support after a reasonable opportunity for further investigation or discovery, SenoRx's customer presentations are false, misleading, and likely to deceive the public as a result of SenoRx's failure to disclose one or more material facts, as for example, the material fact that the FDA cleared labeling for both the predicate MammoSite® device and the Contura™ Multi-Lumen Balloon explicitly warn against specific use with a balloon surface-to-skin surface distance of less than 5 mm.

62. SenoRx's false and misleading representations have confused and misled, and will continue to confuse and mislead a substantial number of persons who receive these misleading representations into believing those representations, such as, for example, that the Contura™ Multi-Lumen Balloon is FDA cleared and/or approved for administration of radiation treatment to superficial resection cavities near the surface of the skin.

63. On information and belief, and based on likely evidentiary support after a reasonable opportunity for further investigation or discovery, SenoRx has made, used, approved, and sponsored these misleading representations in promotional materials that disparage and/or discredit Hologic's MammoSite® Applicator, and misrepresent the comparative superiority of SenoRx's Contura™ Multi-Lumen Balloon.

64. On information and belief, and based on likely evidentiary support after a reasonable opportunity for further investigation or discovery, SenoRx relies on these misleading representations to encourage customers to purchase the Contura™ Multi-Lumen Balloon by suggesting that the Contura™ device treats a patient base (as for example, those patients with superficial excision cavities close to the skin surface) for whom treatment with the MammoSite® Applicator is contraindicated.

65. On information and belief, and based on likely evidentiary support after a reasonable opportunity for further investigation or discovery, SenoRx continues to make such misleading representations with the specific intent that these representations deceive and mislead consumers and

potential consumers of brachytherapy products with the result that they will purchase Contura™ Multi-Lumen Balloons when they would otherwise have purchased MammoSite® Applicators.

66. On information and belief, and based on likely evidentiary support after a reasonable opportunity for further investigation or discovery, SenoRx's acts and practices as described herein have misled and/or deceived and are likely to mislead and/or deceive members of the consuming public with the result that, *inter alia*, they will purchase Contura™ Multi-Lumen Balloons when they would otherwise have purchased MammoSite® Applicators.

67. SenoRx's acts alleged herein are unlawful and fraudulent within the meaning of California's Unfair Competition Law. By reason of SenoRx's acts alleged herein, Hologic has suffered, and will continue to suffer, damage to its business, reputation, and good will. This harm constitutes an injury for which Hologic has no adequate remedy at law.

68. SenoRx's acts of unfair competition have caused and will continue to cause Hologic irreparable harm. If SenoRx's unfair competition is not preliminarily and permanently enjoined, Hologic will suffer irreparable harm that cannot be adequately compensated by a monetary award

69. Hologic is entitled to a judgment enjoining and restraining SenoRx from engaging in further unfair competition, and is further entitled to an award of restitution for SenoRx's unjust enrichment.

COUNT SIX –STATE UNFAIR COMPETITION
(CAL. BUS. & PROF. CODE SECTION 17500 *et seq.*)

70. Hologic incorporates by reference its allegations in Paragraphs 1-69 above.

71. On information and belief, and based on likely evidentiary support after a reasonable opportunity for further investigation or discovery, SenoRx purposefully and intentionally engaged in unfair, deceptive, untrue, and/or misleading advertising in violation of Section 17500 *et seq*. of the California Business & Professions Code.

72. On information and belief, and based on likely evidentiary support after a reasonable opportunity for further investigation or discovery, SenoRx has and is currently advertising its

Contura™ Multi-Lumen Balloon through customer presentations which compare the MammoSite® Applicator and the Contura™ Multi-Lumen Balloon. *See* Exhibit G.

73. On information and belief, and based on likely evidentiary support after a reasonable opportunity for further investigation or discovery, SenoRx through its customer presentations cites purportedly scientifically reliable data to advertise that the Contura™ Multi-Lumen Balloon is superior to the MammoSite® Applicator. SenoRx advertises, for example, that the Contura™ Multi-Lumen Balloon is superior to the MammoSite® Applicator radiation treatment of surgical margins in close proximity to (at, for example, less than 5 mm from) the surface of the skin. (*See* Exhibit G).

74. On information and belief, and based on likely evidentiary support after a reasonable opportunity for further investigation or discovery, such SenoRx's customer presentations are false, misleading, and likely to deceive the public in that SenoRx is advertising capabilities of the Contura™ Multi-Lumen Balloon for which SenoRx has not received FDA clearance or approval. SenoRx, for example, has no brachytherapy device which is FDA cleared or approved for treatment of superficial excision margins in close proximity to the surface of the skin.

75. On information and belief, and based on likely evidentiary support after a reasonable opportunity for further investigation or discovery, SenoRx's customer presentations are false, misleading, and likely to deceive the public as a result of SenoRx's failure to disclose one or more material facts, as for example, the material fact that the FDA cleared labeling for both the predicate MammoSite® device and the Contura™ Multi-Lumen Balloon explicitly warn against specific use with, a balloon surface-to-skin surface distance of less than 5 mm.

76. SenoRx's false and misleading representations have confused and misled, and will continue to confuse and mislead a substantial number of persons who receive these misleading representations into believing those representations, such as, for example, that the Contura™ Multi-Lumen Balloon is FDA cleared and/or approved for administration of radiation treatment to superficial resection cavities near the surface of the skin.

77. On information and belief, and based on likely evidentiary support after a reasonable opportunity for further investigation or discovery, SenoRx has made, used, approved, and sponsored

these misleading representations in promotional materials that disparage and/or discredit Hologic's MammoSite® Applicator, and misrepresent SenoRx's Contura™ Multi-Lumen Balloon.

78. On information and belief, and based on likely evidentiary support after a reasonable opportunity for further investigation or discovery, SenoRx relies on these misleading representations to encourage customers to purchase the Contura™ Multi-Lumen Balloon by suggesting that the Contura™ device treats a patient base (as for example, those patients with superficial excision cavities close to the skin surface) for whom treatment with the MammoSite® Applicator is contraindicated.

79. On information and belief, and based on likely evidentiary support after a reasonable opportunity for further investigation or discovery, SenoRx continues to make such misleading representations with the specific intent that these representations deceive and mislead consumers and potential consumers of brachytherapy products with the result that they will purchase Contura™ Multi-Lumen Balloons when they would otherwise have purchased MammoSite® Applicators.

80. On information and belief, and based on likely evidentiary support after a reasonable opportunity for further investigation or discovery, in making and disseminating the representations described herein, SenoRx knew, or by the exercise of reasonable care should have known, that its representations were untrue or misleading, and were in violation of California Business and Professions Code Section 17500 *et seq*.

81. SenoRx's acts have substantially damaged Hologic's business, substantially damaged consumers' interests, and unjustly enriched SenoRx, and will continue to do so unless enjoined by the Court. If SenoRx's unfair competition is not preliminarily and permanently enjoined, Hologic will suffer irreparable harm that cannot be adequately compensated by a monetary award

82. Hologic is entitled to a judgment enjoining and restraining SenoRx from engaging in further wrongful conduct, and is further entitled to an award of restitution for SenoRx's unjust enrichment.

DEMAND FOR JURY TRIAL

83. Pursuant to Rule 38(b) of the Federal Rules of Civil Procedure and Civil Local Rule 3-6(a), Hologic hereby demands a trial by jury on all issues so triable.

PRAYER FOR RELIEF

WHEREFORE, Hologic prays that this Court grant it the following relief:

(a) enter judgment against SenoRx adjudging the '204, '142, and '813 patents to be valid, enforceable and infringed;

(b) issue a preliminary and permanent injunction against SenoRx for infringement of the '204, '813, and '142 patents pursuant to 35 U.S.C. § 283;

(c) award Hologic an amount adequate to compensate for SenoRx's infringement of the Patents-In-Suit, as provided under 35 U.S.C. § 284;

(d) an adjudication that SenoRx has willfully infringed the Patents-In-Suit and increasing the award of damage to Hologic up to three times in view of SenoRx's willful infringement;

(e) enter judgment requiring that SenoRx and its officers, agents, servants, employees, owners, and representatives, and all other persons, firms, or corporations in active concert or participation with it, be enjoined and restrained from committing further acts of false advertising and unfair competition pursuant to 15 U.S.C. § 1116(a) and California Business & Professions Code § 17203;

(f) award Hologic its actual damages and SenoRx's profits according to proof for SenoRx's Lanham Act violations pursuant to 15 U.S.C. § 1117(a);

(g) award Hologic restitution and recovery of SenoRx's unjust enrichment;

(h) award Hologic prejudgment interest;

(i) a declaration that this is an exceptional case under 35 U.S.C. § 285 and 15 U.S.C. § 1117(a) and that Hologic be awarded its attorneys' fees and costs incurred in prosecuting their claims; and

(j) such other relief as this Court deems proper.

Dated: March 7, 2008

HOWREY LLP

By: /s/ Katharine L. Altemus
Katharine L. Altemus

HOWREY LLP
Attorneys for Plaintiffs
Hologic, Inc., Cytyc Corporation,
and Hologic LP

CERTIFICATE OF SERVICE

I am employed in the County of San Mateo, State of California. I am over the age of 18 and not a party to the within action. My business address is 1950 University Avenue, 4th Floor, East Palo Alto, California 94303.

On March 7, 2008, I served on the interested parties in said action the within:

AMENDED COMPLAINT FOR PATENT INFRINGEMENT, LANHAM ACT VIOLATIONS, AND STATE UNFAIR COMPETITION SEEKING DAMAGES AND INJUNCTIVE RELIEF

F.T. Alexandra Mahaney
Natalie J. Morgan
Wilson Sonsini Goodrich & Rosati
12235 El Camino Real, Suite 200
San Diego, California 92130-3002

Aaron P. Maurer
Adam D. Harber
Bruce R. Genderson
Rachel R. Shanahan
Williams & Connolly, LLP
725 – 12th Street, N.W.
Washington, D.C. 20005

☒ (EMAIL/ELECTRONIC TRANSMISSION) Based on a court order or an agreement of the parties to accept service by e-mail or electronic transmission, I caused the documents to be sent to the persons at the e-mail addresses listed above. I did not receive, within a reasonable time after the submission, any electronic message or other indication that the transmission was unsuccessful.

I declare under penalty of perjury that I am employed in the office of a member of the bar of this Court at whose direction the service was made and that the foregoing is true and correct.

Executed on March 7, 2008, at East Palo Alto, California.

Sonya Schwab
(Type or print name)

Sonya Schwab
(Signature)

Exhibit A

US005913813A

United States Patent [19]

Williams et al.

[11] **Patent Number: 5,913,813**

[45] **Date of Patent: Jun. 22, 1999**

[54] **DOUBLE-WALL BALLOON CATHETER FOR TREATMENT OF PROLIFERATIVE TISSUE**

[75] Inventors: **Jeffery A. Williams**, Baltimore, Md.; **Christopher H. Porter**, Woodinville, Wash.; **Jeffrey F. Williamson**; **James F. Dempsey**, both of St. Louis, Mo.; **Timothy J. Patrick**; **James B. Stubbs**, both of Alpharetta, Ga.

[73] Assignee: **Proxima Therapeutics, Inc.**, Alpharetta, Ga.

[21] Appl. No.: **08/900,021**

[22] Filed: **Jul. 24, 1997**

[51] **Int. Cl.**[6] **A61N 5/00**

[52] **U.S. Cl.** **600/3**

[58] **Field of Search** 600/1–8

[56] **References Cited**

U.S. PATENT DOCUMENTS

3,324,847	6/1967	Zoumboulis .	
5,106,360	4/1992	Ishiwara et al. .	
5,429,582	7/1995	Williams .	
5,611,767	3/1997	Williams .	
5,662,580	9/1997	Bradshaw et al.	600/3
5,782,742	7/1998	Crocker et al. .	
5,785,688	7/1998	Joshi et al. .	

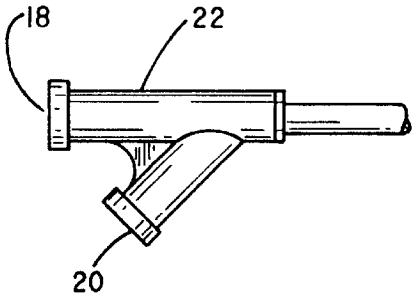
Primary Examiner—John P. Lacyk

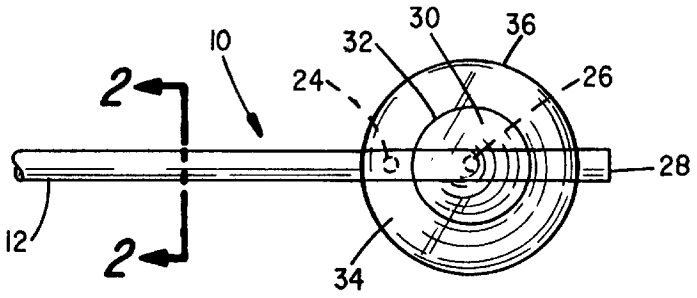
Attorney, Agent, or Firm—Nikolai, Mersereau & Dietz, P.A.

[57] **ABSTRACT**

An instrument for use in brachytherapy comprises a concentric arrangement of inner and outer distensible, spherical chambers disposed near the proximal end of a catheter body where one of the chambers is made to contain a radioactive material with the other chamber containing a radiation absorptive material, the apparatus functioning to provide a more uniform absorbed dose profile in tissue surrounding a cavity created by the removal of a tumor. An alternative embodiment includes non-spherical inner and outer chambers whose respective walls are spaced equidistant over the entire surfaces thereof.

13 Claims, 2 Drawing Sheets





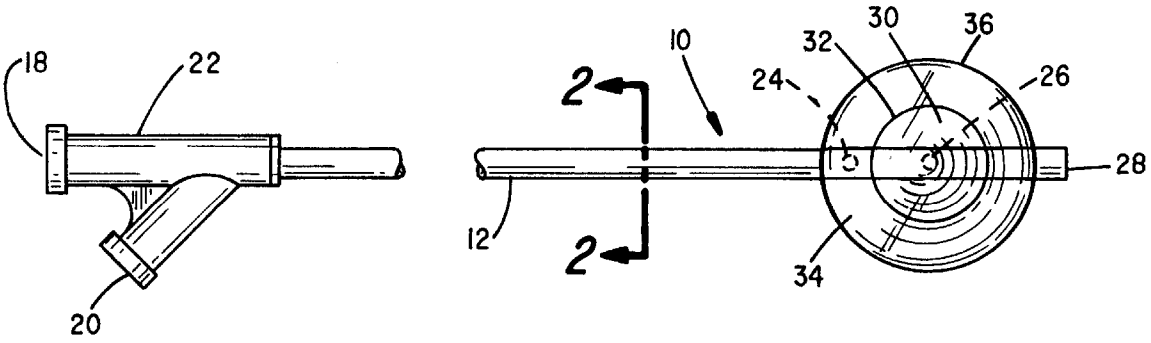


FIG. 1

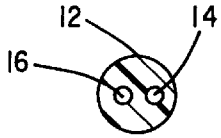


FIG. 2

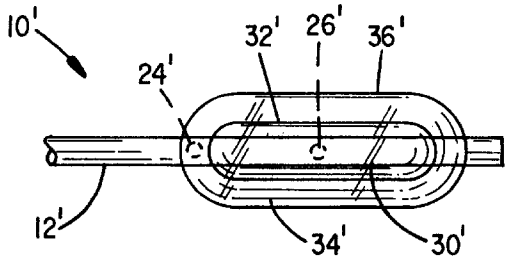


FIG. 3

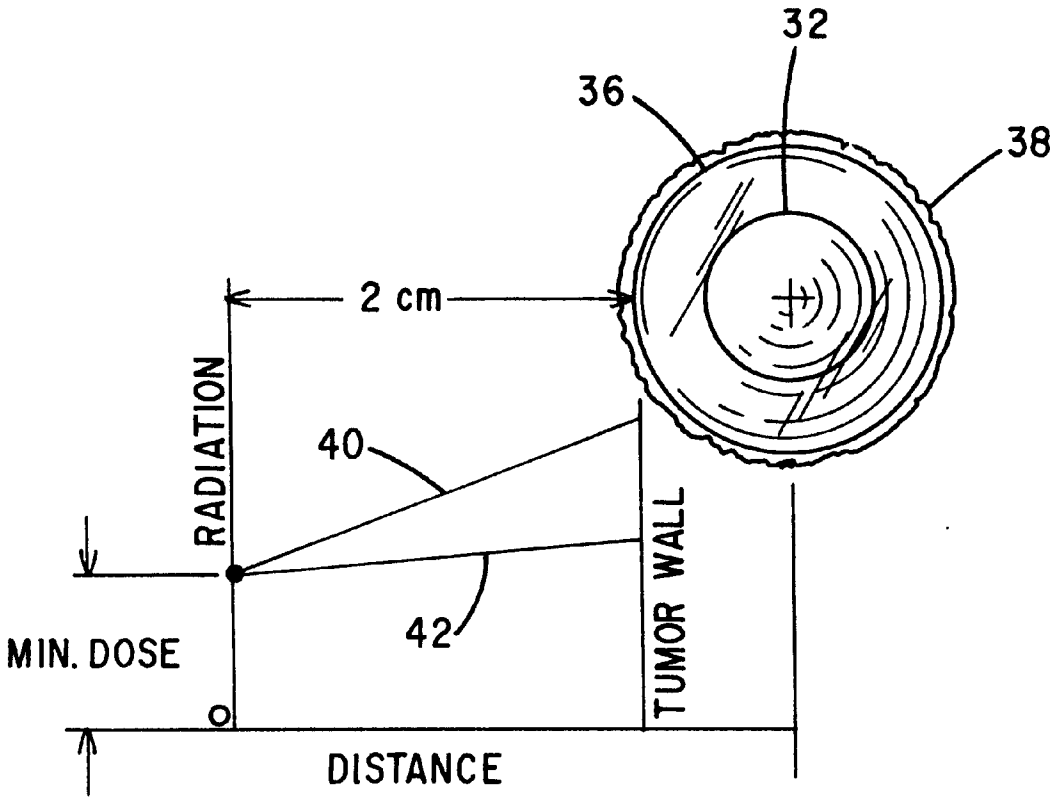


FIG. 4

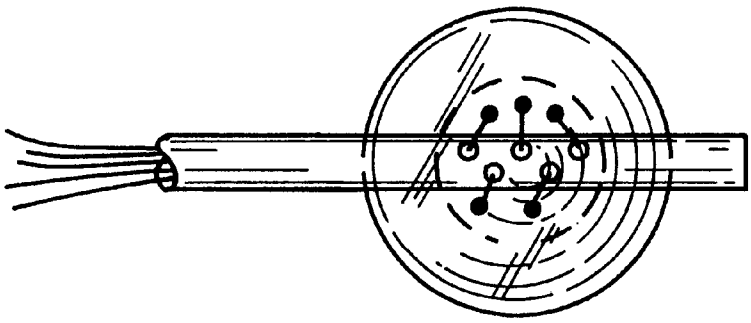


FIG. 5

DOUBLE-WALL BALLOON CATHETER FOR TREATMENT OF PROLIFERATIVE TISSUE

BACKGROUND OF THE INVENTION

I. Field of the Invention

This invention relates generally to apparatus for use in treating proliferative tissue disorders, and more particularly to an apparatus for the treatment of such disorders in the body by the application of radioactive material and/or radiation emissions.

II. Discussion of the Prior Art

In the Williams U.S. Pat. No. 5,429,582 entitled "Tumor Treatment", there is described a method and apparatus for treating tissue surrounding a surgically excised tumor with radioactive emissions to kill any cancer cells that may be present in the margins surrounding the excised tumor. In accordance with that patent, there is provided a catheter having an inflatable balloon at a distal end thereof to define a distensible reservoir. Following surgical removal of a tumor, say in the brain or breast, the deflated balloon may be introduced into the surgically-created pocket left following removal of a tumor and then the balloon is inflated by injecting a fluid having radionuclide(s) therein into the distensible reservoir, via a lumen in the catheter.

When it is considered that the absorbed dose rate at a point exterior to the radioactive source is inversely proportional to the square of the distance between the radiation source and the target point, tissue directly adjacent the wall of the distensible reservoir may be overly "hot" to the point where healthy tissue necrosis may result. In general, the amount of radiation desired by the physician is a certain minimum amount that is delivered to a site 0–3 cms away from the wall of the excised tumor. It is desirable to keep the radiation in the space between that site and the wall of the distensible reservoir as uniform as possible to prevent over-exposure to tissue at or near the reservoir wall. In treating other cancers, such as bladder cancer, where the neoplastic tissue is generally located on the bladder surface, deep penetration is unnecessary and to be avoided.

A need exists for an instrument which may be used to deliver radiation from a radioactive source to target tissue within the human body of a desired intensity and at a predetermined distance from the radiation source without over-exposure of body tissues disposed between the radiation source and the target.

SUMMARY OF THE INVENTION

We have found that it is possible to deliver a desired radiation dose at a predetermined radial distance from a source of radioactivity by providing a first spacial volume at the distal end of a catheter and a second spacial volume defined by a surrounding of the first spatial volume by a polymeric film wall where the distance from the spatial volume and the wall is maintained substantially constant over their entire surfaces. One of the inner and outer volumes is filled with either a fluid or a solid containing a radionuclide(s) while the other of the two volumes is made to contain either a low radiation absorbing material, e.g., air or even a more absorptive material, such as an x-ray contrast fluid. Where the radioactive material comprises the core, the surrounding radiation absorbing material serves to control the radial profile of the radioactive emissions from the particular one of the inner and outer volumes containing the radionuclide(s) so as to provide a more radially uniform radiation dosage in a predetermined volume surrounding the outer chamber. Where the core contains the absorbent material, the radial depth of penetration of the radiation can be tailored by controlling the core size.

DESCRIPTION OF THE DRAWINGS

The foregoing features, objects and advantages of the invention will become apparent to those skilled in the art from the following detailed description of a preferred embodiment, especially when considered in conjunction with the accompanying drawings in which:

FIG. **1** is a side view of an apparatus for delivering radioactive emissions to body tissue;

FIG. **2** is a cross-sectional view taken along the line **2**—**2** in FIG. **1**;

FIG. **3** is a fragmentary side view of an apparatus for administering radiation therapy in accordance with a second embodiment;

FIG. **4** is a graph helpful in understanding the operation of the apparatus of the present invention; and

FIG. **5** depicts a further embodiment of the invention.

DESCRIPTION OF THE PREFERRED EMBODIMENT

Referring first to FIG. **1**, there is indicated generally by numeral **10** a surgical instrument for providing radiation treatment to proliferative tissue in a living patient. It is seen to comprise a tubular body member **12** having first and second lumens **14** and **16** (FIG. **2**) extending from proximal ports **18** and **20** in a molded plastic hub **22** to inflation ports **24** and **26** formed through the side wall of the tube **12** and intersecting with the lumens **14** and **16**, respectively.

Affixed to the tubular body **12** proximate the distal end **28** thereof is an inner spatial volume **30** which may be defined by a generally spherical polymeric film wall **32**. The interior of the chamber **30** is in fluid communication with the inflation port **26**. Surrounding the spatial volume **30** is an outer chamber **34** defined by an outer polymeric film wall **36** that is appropriately spaced from the wall **32** of the inner chamber **30** when the two chambers are inflated or otherwise filled and supported. Chamber **34** encompasses the inflation port **24**.

The embodiment of FIG. **1** can be particularly described as comprising two spherical chambers **30** and **34**, one inside the other. In accordance with a first embodiment of the invention, the outer chamber **34**, being the volume defined by the space between the inner spherical wall **32** and the outer spherical wall **36**, may be filled with air or, alternatively, a radiation absorbing fluid, such as a contrast media used in angiography. The inner chamber **30** is then filled with a material containing a predetermined radionuclide, for example, I-125, I-131, Yb-169 or other source of radiation, such as radionuclides that emit photons, beta particles or other therapeutic rays.

Those skilled in the art will appreciate that instead of having the inner spatial volume **30** defined by a generally spherical polymeric film wall as at **32**, the catheter body member **12** may have a solid spherical radiation emitting material in which event that solid sphere would be surrounded with the outer spherical wall **36** with the spatial volume therebetween occupied by a radioactive ray absorbent material, such as air, water or a contrast material.

It is further contemplated that instead of having the inner spatial volume comprising a single solid sphere, it may instead comprise a plurality of radioactive particles strategically placed within the inner spatial volume so as to radiate

in all directions with a substantially equal intensity. FIG. **5** illustrates a catheter having the inner spatial volume occupied by a plurality of radioactive beads that are mounted on the distal ends of a plurality of wires that are routed through the catheter body and exit a plurality of ports formed through the wall of the catheter body and reaching the lumen. This arrangement allows the exact positioning of the individual radiation sources to be positioned so as to generate a desired resultant profile.

It is not essential to the invention that the chambers **30** and **34** have spherical walls, so long as the spacing between the wall of the inner chamber and the wall of the outer chamber remain generally constant, such as is illustrated in FIG. **3**.

Referring to FIG. **4**, there is shown the two concentric spherical chambers of FIG. **1** defined by inner spherical wall **32** and outer spherical wall **36** disposed within the margin **38** of a surgically excised tumor. It is desired that the radiation emitted from the core **32** be capable of delivering a certain minimum dose absorbed at a location approximately 0–3 cms from the margin **38**. Curve **40** is a plot of absorbed dose vs. radial distance that would be obtained if the inner chamber defined by spherical wall **32** was not present and the entire volume of the spherical chamber defined by wall **36** were filled with the radioactive fluid. Plot **42** reflects the absorbed dose distribution as a function of radial distance when the radioactive fluid is contained within the inner chamber and is surrounded by either a gas or a more radiation absorbing material. Comparing the plots **40** and **42**, by providing the concentric arrangement depicted, the absorbed dose profile in the space between the 2 cm site and the wall of the outer balloon is maintained much more uniform, thus preventing over-treatment of body tissue at or close to the outer wall **36** of the instrument. That is to say, to obtain the same end point absorbed dose at 2 cm, it would be necessary to increase the source activity relative to that used for a completely filled (to surface **36**) configuration, assuming the same radionuclide is used in both configurations.

With no limitation intended, the distensible polymeric chambers may comprise a biocompatible, radiation resistant polymer, such as Silastic rubbers, polyurethanes, polyethylene, polypropylene, polyester, PVC, C-Flex. The radioactive fluid contained within the inner chamber **32** can be made from any solution of radionuclide(s), e.g., a solution of I-125 or I-131. A radioactive fluid can also be produced using a slurry of a suitable fluid containing small particles of solid radionuclides, such as Au-198, Y-90. Moreover, the radionuclide(s) can be embodied in a gel.

In the embodiments heretofore described, the material containing the radionuclide(s) is located in the inner chamber. The invention also contemplates that the outer chamber **34** may contain the material having the radionuclide therein while the inner chamber **30** contains the radiation absorptive material. This configuration is advantageous where a profile exhibiting higher intensity at a tissue surface with lesser penetration is desired. By using this approach, less volume of radioactive material is required than if the entire volume of the device were filled with radioactive material. Moreover, the outer chamber wall need not be spherical, yet a uniform profile is obtainable. Experiments have shown that a steeper radial absorbed source gradient can be obtained using a radiation attenuation fluid in the inner chamber **30** than otherwise obtains when only a single distensible chamber is used, as in the aforereferenced Williams U.S. Pat. No. 5,429,582. The invention also contemplates that the radioactive material in the inner core can be replaced by a core containing solid radionuclide-containing particles. For example, radioactive micro spheres of the type available from the 3M Company of St. Paul, Minn., may be used in place of the fluid. This radioactive source can either be preloaded into the catheter at the time of manufacture or loaded into the device after it has been implanted into the space formerly occupied by the excised tumor. Such a solid radioactive core configuration offers the advantage in that it allows a wider range of radionuclides than if one is limited to liquids. Solid radionuclides that could be used with the delivery device of the present invention are currently generally available as brachytherapy radiation sources.

In either the concentric spherical embodiment of FIG. **1** or the non-spherical configuration of FIG. **3**, the spacing between the inner and outer chambers needs to be held somewhat constant to avoid "hot spots". This result can be achieved by careful placement of precision blown polymer parisons or by using compressible foams or mechanical spacers in the form of webs joining the inner wall **32** to the outer wall **36**.

This invention has been described herein in considerable detail in order to comply with the patent statutes and to provide those skilled in the art with the information needed to apply the novel principles and to construct and use such specialized components as are required. However, it is to be understood that the invention can be carried out by specifically different equipment and devices, and that various modifications, both as to the equipment and operating procedures, can be accomplished without departing from the scope of the invention itself.

What is claimed is:

1. Apparatus for delivering radioactive emissions to a body location with a uniform radiation profile, comprising:

(a) a catheter body member having a proximal end and distal end;

(b) an inner spatial volume disposed proximate the distal end of the catheter body member;

(c) an outer, closed, inflatable, chamber defined by a radiation transparent wall affixed to the body member proximate the distal end thereof in surrounding relation to the inner spatial volume with a predetermined constant spacing between said inner spatial volume and the radiation transparent wall;

(d) a material containing a radionuclide(s) disposed in one of the inner spatial volume and outer chamber; and

(e) means disposed in the other of the inner spatial volume and outer chamber for rendering uniform the radial absorbed dose profile of the emissions from the one of the inner spatial volume and outer chamber containing the radionuclides.

2. The apparatus as in claim **1** wherein said inner spatial volume is an inner closed, chamber defined by a further radiation transparent wall.

3. The apparatus of claim **1** wherein the means for rendering uniform the absorbed dose profile is a radiation attenuating material.

4. The apparatus of claim **3** wherein the radiation attenuating material is selected from a group consisting of barium sulphate, water, and X-ray contrast media.

5. The apparatus as in claim **2** wherein the radionuclide is in a fluid form.

6. The apparatus as in claim **5** wherein the fluid comprises an isotope of iodine.

7. The apparatus as in claim **1** wherein the radionuclide is a slurry of a fluid containing particles of a solid isotope.

8. The apparatus as in claim **2** wherein the inner chamber contains the radioactive material.

9. The apparatus as in claim **1** wherein the outer chamber contains the radioactive material.

10. The apparatus as in claim **8** wherein the radioactive material is a fluid.

11. The apparatus as in claim **8** wherein the radioactive material is a solid.

12. The apparatus as in claim **1** wherein the material containing a radionuclide comprises a plurality of radioactive solid particles placed at predetermined locations within the inner spatial volume to provide a desired composite radiation profile.

13. The apparatus as in claim **2** wherein the inner and outer chambers are spherical in shape and are concentric.

* * * * *

Exhibit B

(12) **United States Patent**
Winkler et al.

(10) **Patent No.: US 6,413,204 B1**
(45) **Date of Patent: *Jul. 2, 2002**

(54) **INTERSTITIAL BRACHYTHERAPY APPARATUS AND METHOD FOR TREATMENT OF PROLIFERATIVE TISSUE DISEASES**

(75) Inventors: **Rance A. Winkler**, Atlanta; **Timothy J. Patrick**; **James Stubbs**, both of Alpharetta, all of GA (US)

(73) Assignee: **Proxima Therapeutics, Inc.**, Alpharetta, GA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **09/293,524**

(22) Filed: **Apr. 15, 1999**

Related U.S. Application Data

(63) Continuation-in-part of application No. 08/900,021, filed on Jul. 4, 1997, now Pat. No. 5,913,813.

(51) **Int. Cl.**[7] **A61N 5/00**
(52) **U.S. Cl.** **600/3**
(58) **Field of Search** 600/1–8

(56) **References Cited**

U.S. PATENT DOCUMENTS

3,324,847 A	6/1967	Zoumboulis	.....	128/1.2
3,872,856 A	3/1975	Clayton	.....	128/1.2
4,417,576 A	11/1983	Baran	.....	128/207.15
4,706,652 A	11/1987	Horowitz	.....	128/1.2
4,754,745 A	7/1988	Horowitz	.....	128/1.2
4,763,642 A	8/1988	Horowitz	.....	128/1.2

(List continued on next page.)

FOREIGN PATENT DOCUMENTS

EP	0340881	11/1989	..... A61N/5/10
EP	0867200	9/1998	
GB	2105201	3/1983	..... A61N/1/06
WO	9210932	7/1992	..... A61N/5/02
WO	9309724	5/1993	..... A61B/17/36
WO	9719723	6/1997	..... A61N/5/00
WO	9812979	4/1998	..... A61B/19/00
WO	9911325	3/1999	
WO	9933515	7/1999	
WO	9942163	9/1999	

OTHER PUBLICATIONS

A. Bex et al., *A System for Focal Intracavitary Irradiation of Bladder Cancer with Remote Iridium–192 Afterloading*, 21 Eur Urol 1992, 245–249 (1992).

Ashpole, R.D. et al., "A New Technique of Brachtherapy for Malignant Gliomas with Caesium–137: A New Method Utilizing a Remote Afterloading System," Clinical Oncology, vol. 2, 333–7 (1990).

Chun, M. et al., "Interstitial Iridium–192 Implantation for Malignant Brain Tumours. Part II: Clinical Experience," *The British Journal of Radiology*, vol. 62, 158–62 (1989).

Garfield, J. et al., "Postoperative Intracavitary Chemotherapy of Malignant Gliomas," *J. Neurosurg.*, vol. 39, 315–22 (Sep. 1973).

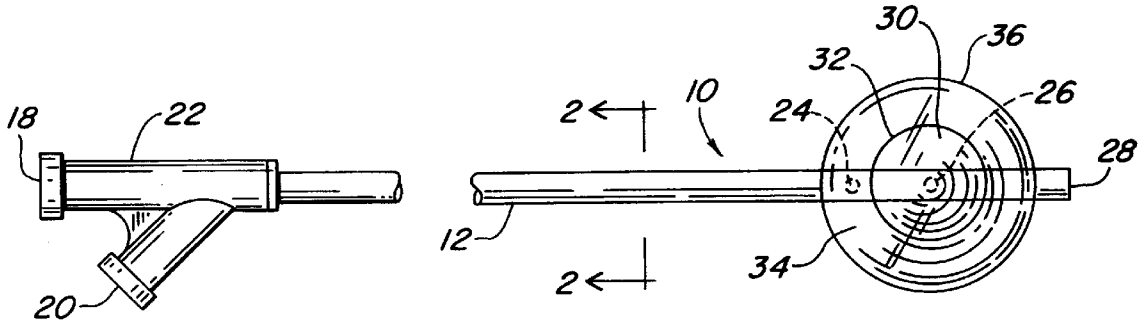
(List continued on next page.)

Primary Examiner—John P. Lacyk
(74) *Attorney, Agent, or Firm*—Thomas J. Engellenner; Ronald E. Cahill; Nutter, McClennen & Fish, LLP

(57) **ABSTRACT**

An interstitial brachytherapy apparatus for delivering radioactive emissions to an internal body location includes a catheter body member having a proximal end and distal end, an inner spatial volume disposed proximate to the distal end of the catheter body member, an outer spatial volume defined by an expandable surface element disposed proximate to the distal end of the body member in a surrounding relation to the inner spatial volume, and a radiation source disposed in the inner spatial volume.

36 Claims, 3 Drawing Sheets



U.S. PATENT DOCUMENTS

4,821,725	A		4/1989	Azam et al. ..... 128/420 A
4,867,741	A		9/1989	Portnoy 604/10
5,084,001	A		1/1992	Van't Hooft et al. 600/3
5,084,015	A		1/1992	Moriuchi 604/96
5,106,360	A		4/1992	Ishiwara et al. 600/2
5,112,303	A		5/1992	Pudenz et al. 604/49
5,152,747	A		10/1992	Olivier 604/93
5,236,410	A		8/1993	Granov et al. 600/12
5,429,582	A		7/1995	Williams 600/2
5,484,384	A		1/1996	Fearnot 600/3
5,503,613	A		4/1996	Weinberger 600/3
5,566,221	A		10/1996	Smith et al. 378/145
5,611,767	A		3/1997	Williams 600/2
5,662,580	A		9/1997	Bradshaw et al. 600/3
5,707,332	A		1/1998	Weinberger 600/3
5,713,828	A		2/1998	Coniglione 600/7
5,720,717	A		2/1998	D'Andrea 604/21
5,764,723	A		6/1998	Weinberger et al. 378/65
5,782,742	A		7/1998	Crocker et al. 600/3
5,785,688	A		7/1998	Joshi et al. 604/141
5,913,813	A	*	6/1999	Williams et al. 600/3
5,924,973	A	*	7/1999	Wenberger 600/3
6,036,631	A		3/2000	McGrath et al. 600/3
6,059,812	A	*	5/2000	Clerc et al. 600/3

OTHER PUBLICATIONS

Gutin, P. et al., "Brachytherapy of Recurrent Malignant Brain Tumors With Removable High–Activity Iodine–125 Sources," *J. Neurosurg.*, vol. 60, 61–8 (1984).

Johannesen, T.B. et al., "Intracavity Fractionated Balloon Brachytherapy in Gilioblastoma," *Acta Neurochir* (*Wien*), vol. 141, 127–33 (1999).

Leibel, S. et al., "The Integration of Interstitial Implantation Into the Preliminary Mangement of Patients With Malignant Gliomas: Results of a Phase II Northern California Oncology Group Trial," *Am. J. Clin. Oncol.* (*CCT*), vol. 10, No. 2, p. 106 (1987).*

Roberts, D. et al., "Interstitial Hyperthermia and Iridium Brachytherapy in Treamtnet of Malignant Glioma," *J. Neurosurg.*, vol. 64, 581–7 (1986).*

Wu, A. et al., "Interstitial Iridium–192 Implantation for Malignant Brain Tumours, Part 1: Techniques of Dosimetry Planning," *The British Journal of Radiology*, vol. 62, 154–7 (1989).*

* cited by examiner

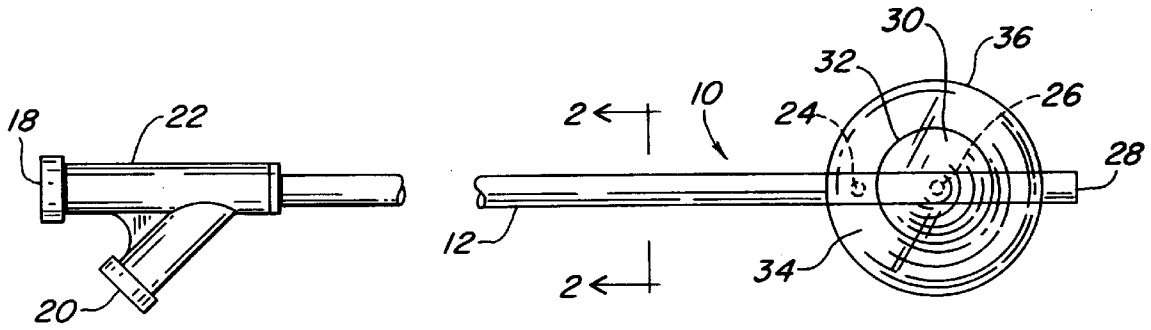


FIG. 1

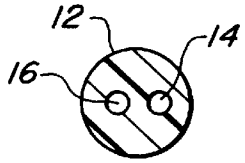


FIG. 2

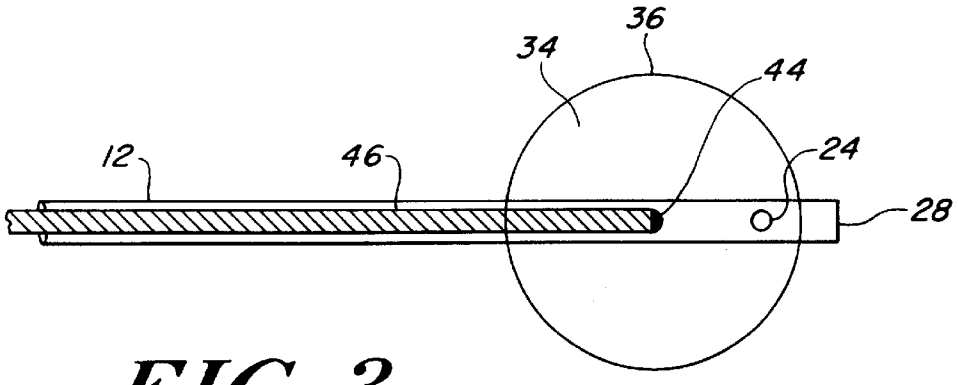


FIG. 3

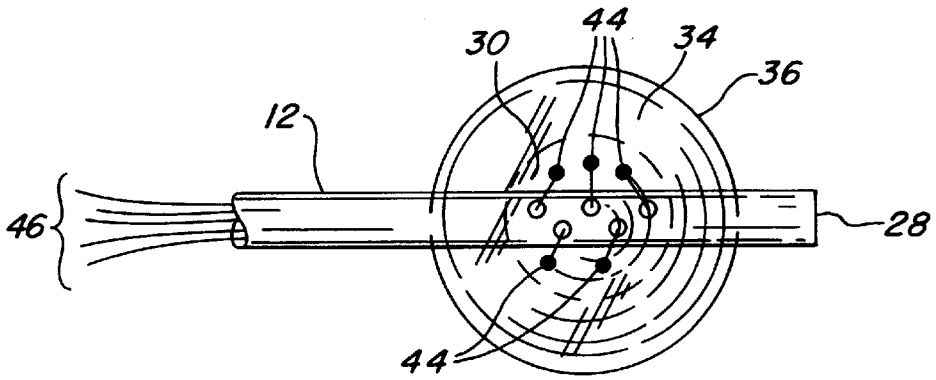


FIG. 4

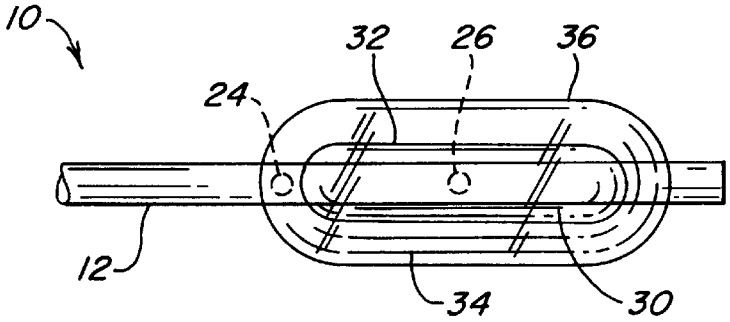


FIG. 5

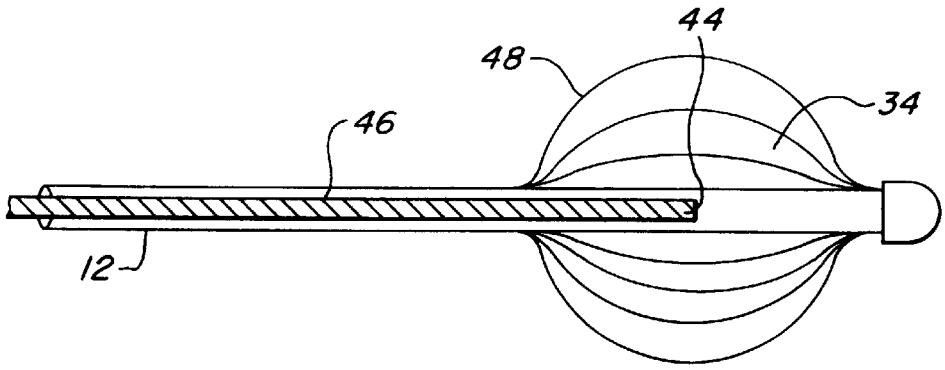


FIG. 6

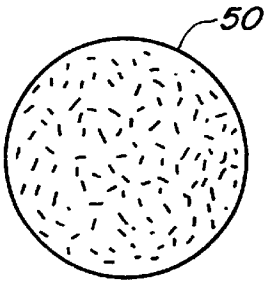


FIG. 7A

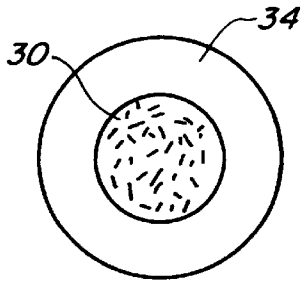


FIG. 7B

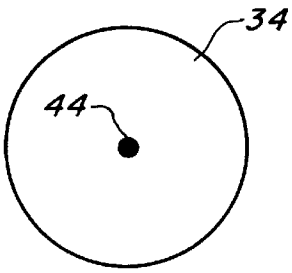


FIG. 7C

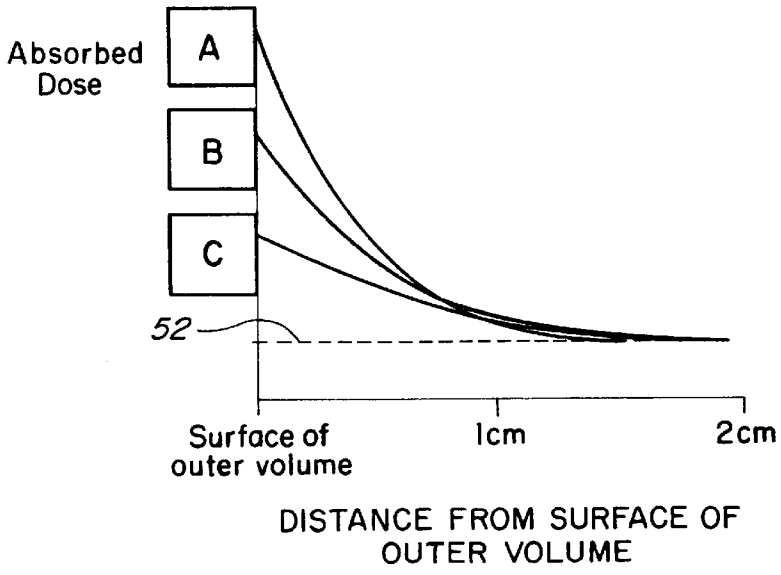


FIG. 7D

INTERSTITIAL BRACHYTHERAPY APPARATUS AND METHOD FOR TREATMENT OF PROLIFERATIVE TISSUE DISEASES

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation-in-part of U.S. patent application Ser. No. 08/900,021, filed Jul. 24, 1997, now U.S. Pat. No. 5,913,813 the contents of which are specifically incorporated herein by reference.

BACKGROUND OF THE INVENTION

The invention relates generally to apparatus for use in treating proliferative tissue disorders, and more particularly to an apparatus for the treatment of such disorders in the body by the application of radiation.

Malignant tumors are often treated by surgical resection of the tumor to remove as much of the tumor as possible. Infiltration of the tumor cells into normal tissue surrounding the tumor, however, can limit the therapeutic value of surgical resection because the infiltration can be difficult or impossible to treat surgically. Radiation therapy can be used to supplement surgical resection by targeting the residual tumor margin after resection, with the goal of reducing its size or stabilizing it. Radiation therapy can be administered through one of several methods, or a combination of methods, including external-beam radiation, stereotactic radiosurgery, and permanent or temporary interstitial brachytherapy. The term "brachytherapy," as used herein, refers to radiation therapy delivered by a spatially confined radioactive material inserted into the body at or near a tumor or other proliferative tissue disease site. Owing to the proximity of the radiation source, brachytherapy offers the advantage of delivering a more localized dose to the target tissue region.

For example, brachytherapy is performed by implanting radiation sources directly into the tissue to be treated. Brachytherapy is most appropriate where 1) malignant tumor regrowth occurs locally, within 2 or 3 cm of the original boundary of the primary tumor site; 2) radiation therapy is a proven treatment for controlling the growth of the malignant tumor; and 3) there is a radiation dose-response relationship for the malignant tumor, but the dose that can be given safely with conventional external beam radiotherapy is limited by the tolerance or normal tissue. In brachytherapy, radiation doses are highest in close proximity to the radiotherapeutic source, providing a high tumor dose while sparing surrounding normal tissue. Interstitial brachytherapy is useful for treating malignant brain and breast tumors, among others.

Interstitial brachytherapy is traditionally carried out using radioactive seeds such as ^{125}I seeds. These seeds, however, produce inhomogeneous dose distributions. In order to achieve a minimum prescribed dosage throughout a target region of tissue, high activity seeds must be used, resulting in very high doses being delivered in some regions in proximity to the seed or seeds which can cause radionecrosis in healthy tissue.

Williams U.S. Pat. No. 5,429,582, entitled "Tumor Treatment," describes a method and apparatus for treating tissue surrounding a surgically excised tumor with radioactive emissions to kill any cancer cells that may be present in the tissue surrounding the excised tumor. In order to implement the radioactive emissions, Williams provides a catheter having an inflatable balloon at its distal end that defines a distensible reservoir. Following surgical removal of a tumor, the surgeon introduces the balloon catheter into the surgically created pocket left following removal of the tumor. The balloon is then inflated by injecting a fluid having one or more radionuclides into the distensible reservoir via a lumen in the catheter.

The apparatus described in Williams solves some of the problems found when using radioactive seeds for interstitial brachytherapy, but leaves some problems unresolved. The absorbed dose rate at a target point exterior to a radioactive source is inversely proportional to the square of the distance between the radiation source and the target point. As a result, where the radioactive source has sufficient activity to deliver a prescribed dose, say 2 centimeters into the target tissue, the tissue directly adjacent the wall of the distensible reservoir, where the distance to the radioactive source is very small, may still be overly "hot" to the point where healthy tissue necrosis may result. In general, the amount of radiation desired by the physician is a certain minimum amount that is delivered to a region up to about two centimeters away from the wall of the excised tumor. It is desirable to keep the radiation that is delivered to the tissue in the target treatment region within a narrow absorbed dose range to prevent over-exposure to tissue at or near the reservoir wall, while still delivering the minimum prescribed dose at the maximum prescribed distance from the reservoir wall.

There is still a need for an instrument which can be used to deliver radiation from a radioactive source to target tissue within the human body with a desired intensity and at a predetermined distance from the radiation source without over-exposure of body tissues disposed between the radiation source and the target.

SUMMARY OF THE INVENTION

The present invention solves the problems described above by providing an interstitial brachytherapy apparatus for delivering radioactive emissions to an internal body location. The apparatus includes a catheter body member having a proximal end and distal end, an inner spatial volume disposed proximate to the distal end of the catheter body member, an outer spatial volume defined by an expandable surface element disposed proximate to the distal end of the body member in a surrounding relation to the inner spatial volume, and a radiation source disposed in the inner spatial volume. The inner and outer spatial volumes are configured to provide an absorbed dose within a predetermined range throughout a target tissue. The target tissue is located between the outer spatial volume expandable surface and a minimum distance outward from the outer spatial volume expandable surface. The predetermined dose range is defined as being between a minimum prescribed absorbed dose for delivering therapeutic effects to tissue that may include cancer cells, and a maximum prescribed absorbed dose above which healthy tissue necrosis may result.

In different embodiments, the inner spatial volume can be defined by a distensible polymeric wall containing radioactive source material which can be a fluid material, by a solid radioactive source, or by a region containing a plurality of solid radioactive sources. The outer spatial volume is defined by an expandable surface element that may be, for example, an inflatable polymeric wall or an expandable cage. The expandable surface element can cause tissue to conform to its intended shape, and preferably, the apparatus creates absorbed isodose profiles in the target tissue that are substantially similar in shape to the expandable surface element in substantially three dimensions.

The invention also provides a method for treating a proliferating tissue disease using interstitial brachytherapy at an internal body location. The method includes surgically creating access to the proliferating tissue within a patient and surgically resecting at least a portion of the proliferating tissue to create a resection cavity within body tissue. An interstitial brachytherapy apparatus for delivering radioactive emissions as described above is then provided and intra-operatively placed into the resection cavity. After a prescribed absorbed dose has been delivered to tissue surrounding the apparatus, the apparatus is removed. The radioactive source material may be placed into the interstitial brachytherapy apparatus after the apparatus is placed in the resection cavity, and may be removed before the apparatus is removed. The method has particular applications to brain and breast cancers.

DESCRIPTION OF THE DRAWINGS

The foregoing features, objects and advantages of the invention will become apparent to those skilled in the art from the following detailed description of a preferred embodiment, especially when considered in conjunction with the accompanying drawings in which:

FIG. **1** is a side view of an interstitial brachytherapy apparatus of the invention for delivering radioactive emissions to body tissue;

FIG. **2** is a cross-sectional view taken along the line **2**—**2** in FIG. **1**;

FIG. **3** is an additional embodiment of an interstitial brachytherapy apparatus of the invention having a solid radiation source;

FIG. **4** is an additional embodiment of an interstitial brachytherapy apparatus of the invention having a radiation source comprising a plurality of solid radiation particles;

FIG. **5** depicts a further embodiment of the invention wherein the inner and outer spatial volumes of the interstitial brachytherapy apparatus are non-spherical;

FIG. **6** illustrates an interstitial brachytherapy apparatus of the invention having an expandable outer spatial volume surface; and

FIGS. **7**A–D illustrate the absorbed dose versus distance into target tissue for several interstitial brachytherapy apparatus configurations.

DESCRIPTION OF THE PREFERRED EMBODIMENT

A surgical instrument **10** for providing radiation treatment to proliferative tissue in a living patient is illustrated in FIG. **1**. Surgical instrument **10** includes a tubular body member **12** having first and second lumens **14** and **16** (FIG. **2**) extending from proximal ports **18** and **20** in a molded plastic hub **22** to inflation ports **24** and **26** formed through the side wall of the tube **12** and intersecting with the lumens **14** and **16**, respectively.

Affixed to the tubular body **12** proximate the distal end **28** thereof is an inner spatial volume **30** which may be defined by a generally spherical polymeric film wall **32**. The interior of the inner volume **30** is in fluid communication with the inflation port **26**. Surrounding inner spatial volume **30** is an outer spatial volume **34** defined by an outer polymeric film wall **36** that is appropriately spaced from the wall **32** of the inner spatial volume **30** when the two volumes are inflated or otherwise supported. Outer volume **34** encompasses inflation port **24**. With no limitation intended, the distensible polymeric film walls may comprise a biocompatible, radiation resistant polymer, such as silastic rubbers, polyurethanes, polyethylene, polypropylene, polyester, or PVC.

The embodiment of FIG. **1** includes inner and outer spatial volumes **30** and **34**, one inside the other. The outer spatial volume **34**, being the volume defined by the space between the inner spherical wall **32** and the outer spherical wall **36**, may be filled with air or, alternatively, a radiation absorbing fluid, such as a contrast media used in angiography. The inner volume **30** is then filled with a material containing a predetermined radionuclide, for example, I-125, I-131, Yb-169 or other source of radiation, such as radionuclides that emit photons, beta particles, gamma radiation, or other therapeutic rays. The radioactive material contained within the inner chamber **32** can be a fluid made from any solution of radionuclide(s), e.g., a solution of I-125 or I-131. A radioactive fluid can also be produced using a slurry of a suitable fluid containing small particles of solid radionuclides, such as Au-198, Y-90. Moreover, the radionuclide(s) can be embodied in a gel. One radioactive material useful in the invention is Iotrex™, a sterile single use, non-pyrogenic solution containing sodium 3-(^{125}I)iodo-4-hydroxybenzenesulfonate (^{125}I-HBS), available from Proxima Therapuetics, Inc. of Alpharetta, Ga.

As an alternative method of providing radioactive source material, such material may be coated on, chemically bonded to, or copolymerized with the material forming inner spherical wall **32**.

Where the radioactive source material is provided as a fluid or gel within inner spherical wall **32**, it may be desirable to provide a solid outer spherical wall **36**. Should inner spherical wall **32** rupture, the radioactive source material will be retained within outer spherical wall **36** and will not leak into the patient. For further safety, the burst strength of inner spherical wall **32** may be designed so as to be lower than that of outer spherical wall **36**. In this way, inner spherical wall **32** will rupture under stress first, releasing its contents into the larger combined space of the inner and outer volumes **30**, **34** and releasing any pressure built up within the inner spherical wall **32** and reducing the risk that radioactive material will spill into the patient. In the event of such a rupture, radioactive fluid could be drained from the apparatus through port **24** by way of lumen **14**, and also from port **26** by way of lumen **16**.

In a further embodiment, illustrated in FIG. **3**, instead of having the inner spatial volume **30** defined by a generally spherical polymeric film wall as at **32**, the catheter body member **12** may have a solid spherical radiation emitting material **44** as the inner spatial volume **30**. For example, radioactive micro spheres of the type available from the 3M Company of St. Paul, Minn., may be used. This radioactive source can either be preloaded into the catheter at the time of manufacture or loaded into the device after it has been implanted into the space formerly occupied by the excised tumor. The solid radiation emitting material **44** can be inserted through catheter **12** on a wire **46**, for example, using an afterloader (not shown). Such a solid radioactive core configuration offers an advantage in that it allows a wider range of radionuclides than if one is limited to liquids. Solid radionuclides that could be used with the delivery device of the present invention are currently generally available as brachytherapy radiation sources. In this embodiment solid spherical inner spatial volume **30** is surrounded by outer spherical wall **36**, defining outer spatial volume **34** between the outer spherical wall **36** and the inner spatial volume **30** with the outer spatial volume **34** occupied by a radioactive ray absorbent material, such as air, water or a contrast material.

In a further embodiment, illustrated in FIG. **4**, inner spatial volume **30**, instead of comprising a single solid sphere, may comprise a plurality of radiation emitting particles **44** strategically placed within the inner spatial volume **30** so as to radiate in all directions with a substantially equal intensity. This plurality of radiation emitting particles **44** can be mounted on the distal ends of a plurality of wires **46** that are routed through the catheter body **12** and exit a plurality of ports formed through the wall of the catheter body and reaching the lumen. This arrangement allows the exact positioning of the individual radiation sources **44** to be positioned so as to generate a desired resultant profile.

As illustrated in FIG. **5**, it is not essential to the invention that the volumes **30** and **34** have spherical walls, so long as the resultant dosing profile is consistent with the shape of the outer volume **34**. That is, the absorbed dose within the target tissue at points equidistant from the surface **36** of the outer spatial volume **34** should be substantially uniform in substantially every direction. Put another way, the three dimensional isodose profiles generated by the radiation source should be substantially similar in shape to the outer spatial volume **34**. Where the inner and outer spatial volumes are created by inflatable membranes and one of the volumes contains a fluid radiation source, this can be achieved by ensuring that the spacing between the wall of the inner volume and the wall of the outer volume remain generally constant. In either the concentric spherical embodiment of FIG. **1** or the non-spherical configuration of FIG. **5**, this result can be achieved by careful placement of precision blown or molded polymer partitions or by using compressible foams or mechanical spacers in the form of webs joining the inner wall **32** to the outer wall **36**. The desired isodose profiles conforming to the shape of the outer spatial volume **34** can also be obtained, for example, by strategic placement of a plurality of radioactive particle sources within the inner spatial volume **30**. Where the apparatus of the invention is deployed in soft tissue, it may also be important for the surface **36** of the outer spatial volume **34** to be sufficiently firm so as to force the target tissue to take on the shape of the surface **36** so that the desired relationship between the isodose profiles and the target tissue is achieved.

When used in an interstitial application, the surface of the outer spatial volume **34** must establish a relationship between the inner spatial volume **30** and the target tissue so as to achieve the aforementioned isodose profile, however, the surface of the outer volume need not be a solid material. For example, as illustrated in FIG. **6**, the surface of the outer volume **34** could be an expandable cage **48** formed from a shape memory metal, such as nitinol, or a suitable plastic, such as an expandable polyethylene cage. Such a cage can be formed in the desired shape to conform to a particular isodose profile, then be contracted for delivery to the target site in vivo, then expanded to cause the tissue surrounding the surgically resected region to take the appropriate shape. The size of the outer spatial volume **34** generally will correspond approximately to the amount of tissue resected, or be slightly larger, allowing the expandable surface of the outer spatial volume to urge tissue on the surface of the resected region into the appropriate shape to promote an even dose distribution around the outer spatial volume in the target tissue. In typical applications, the outer spatial volume has a diameter of approximately 2 to 4 centimeters. In these same applications, where the radiation source is provided as a fluid within an inner balloon, the inner balloon generally has a diameter of approximately 0.5 to 3 centimeters.

FIGS. **7**A–D illustrate the ability of an interstitial brachytherapy apparatus of the invention to deliver a minimum prescribed dose within target tissue while avoiding necrosis inducing radiation "hot spots" in tissue proximate to the apparatus. FIG. **7**A illustrates an interstitial brachytherapy apparatus (device A) such as those employed in U.S. Pat. No. 5,429,582, having a single spatial volume **50** filled with a radioactive material in solution. FIG. **7**B illustrates an interstitial brachytherapy apparatus (device B) of the invention having a first, inner spatial volume **30** filled with a radioactive material in solution and defined by membrane **32**, and a second, outer spatial volume **34** defined by membrane **36** that is substantially evenly spaced apart from membrane **32** in substantially three dimensions. FIG. **7**C illustrates an additional interstitial brachytherapy apparatus (device C) of the invention having a solid, spherical radiation source **44** as the inner spatial volume and a spherical outer spatial volume **34** defined by membrane **36**.

Each of the devices illustrated in FIGS. **7**A–C can be configured to deliver a substantially uniform dose at a given distance into the target tissue from the surface of the outer spatial volume **34** (or from single spatial volume **50** for device A) and to deliver a minimum prescribed dose within a given prescribed depth range into the tissue from the surface of the outer spatial volume **34**. However, the different devices provide very different dose profiles as a function of distance from the surface of the outer volume as illustrated in FIG. **7**D. FIG. **7**D plots the absorbed dose at a given distance into the target tissue from the surface of the outer spatial volume **34** for each of the devices A, B, and C.

Each device can deliver a minimum prescribed dose **52** at a given distance from the surface of the outer spatial volume. For example, device A can readily be configured to provide a dose in a therapeutic range, say between 40 to 60 Gray, at a distance between 0.5 and 1.0 cm from the outer spatial volume for an outer spatial volume having a diameter of 4.0 cm and being in contact with the resection cavity wall. In a typical embodiment, the radioactive source material ranges from approximately 150 to 450 mCi in activity and encompasses most of the target treatment area with a 0.4 to 0.6 Gray/hour isodose contour. At this treatment rate, treatment may be completed in approximately 3 to 7 days, or more commonly, in approximately 3 to 5 days.

In order to reach the minimum prescribed dosage at this distance, however, device A must provide a dose proximate to the surface of the outer spatial volume that is substantially larger than the minimum prescribed dose. For the 4.0 cm diameter outer spatial volume example, the absorbed dosage would be approximately 131 Gray at the outer spatial volume surface. Ideally, radiation therapy should make use the inherent difference in radiosensitivity between the tumor and the adjacent normal tissues to destroy cancerous tissue while causing minimal disruption to surrounding normal tissues. At high doses of radiation, however, the percentage of exposed cells that survive treatment decreases with first-order kinetics in proportion to increasing radiation dose. With increasing cell death comes increasing risk of necrosis or tissue death in healthy tissue that is treated with a high dose of radiation. Accordingly, it is desirable to keep the maximum radiation dose delivered by the brachytherapy apparatus as low as possible while still delivering the desired therapeutic dose to the desired range of tissue.

Comparing the plots A, B, and C, the absorbed dose profile in the space between the 2 cm site and the surface of the outer spatial volume for the devices of the invention is maintained in a much narrower range, preventing over-treatment of body tissue at or close to the surface of the outer volume of the device. Because devices B and C provide an outer spatial volume **34** between the radioactive source and

the target tissue, these devices can use hotter radiation sources to reach the minimum prescribed dosage, but take advantage of the distance between the radioactive source and the target tissue provided by the outer spatial volume **34** to reduce or eliminate hot spots in the target tissue.

Returning to the 4.0 cm diameter outer spatial volume example, if the radiation source is contained within an inner spatial volume, say a solid radioactive sphere such as device C, the absorbed dose profile becomes much different. If the radiation source is configured to provide the same 60 Gray dose at 0.5 cm into the target tissue, the absorbed dose at the outer spatial volume surface is only 94 Gray—a significant decrease from the 131 Gray dose for a type A device. In addition, the treatment range for the type C device will be extended under these circumstance as compared to the type A device, delivering a 40 Gray dose beyond 1.0 cm into the target tissue and delivering approximately double the dose at 3.0 cm into the target tissue. In one embodiment, the inner and outer spatial volumes are configured to control the absorbed dose at the outer spatial volume surface so that the absorbed dose is no greater than about 100 Gray while providing a therapeutic absorbed dose into the target tissue at the desired range. The capability of the apparatus of the invention to deliver absorbed doses deeper into the target tissue than prior interstitial brachytherapy devices while controlling the dose in proximity to the apparatus to reduce or eliminate the risk of healthy tissue necrosis allows for the use of brachytherapy in a greater number of cases.

The interstitial brachytherapy apparatus of the invention can be used in the treatment of a variety of malignant tumors, and is especially useful for in the treatment of brain and breast tumors.

Many breast cancer patients are candidates for breast conservation surgery, also known as lumpectomy, a procedure that is generally performed on early stage, smaller tumors. Breast conservation surgery is typically followed by postoperative radiation therapy. Studies report that 80% of breast cancer recurrences after conservation surgery occur near the original tumor site, strongly suggesting that a tumor bed "boost" of local radiation to administer a strong direct dose may be effective in killing any remaining cancer and preventing recurrence at the original site. Numerous studies and clinical trials have established equivalence of survival for appropriate patients treated with conservation surgery plus radiation therapy compared to mastectomy.

Surgery and radiation therapy are the standard treatments for malignant solid brain tumors. The goal of surgery is to remove as much of the tumor as possible without damaging vital brain tissue. The ability to remove the entire malignant tumor is limited by its tendency to infiltrate adjacent normal tissue. Partial removal reduces the amount of tumor to be treated by radiation therapy and, under some circumstances, helps to relieve symptoms by reducing pressure on the brain.

A method according to the invention for treating these and other malignancies begins by surgical resection of a tumor site to remove at least a portion of the cancerous tumor and create a resection cavity. Following tumor resection, but prior to closing the surgical site, the surgeon intraoperatively places an interstitial brachytherapy catheter apparatus, having an inner spatial volume and an outer spatial volume as described above but without having the radioactive source material loaded, into the tumor resection cavity. Once the patient has sufficiently recovered from the surgery, the interstitial brachytherapy catheter is loaded with a radiation source. The radioactive source dwells in the catheter until the prescribed dose of radiotherapy is delivered, typically for approximately a week or less. The radiation source is then retrieved and the catheter is removed. The radiation treatment may end upon removal of the brachytherapy apparatus, or the brachytherapy may be supplemented by further doses of radiation supplied externally.

It will be understood that the foregoing is only illustrative of the principles of the invention, and that various modifications can be made by those skilled in the art without departing from the scope and spirit of the invention. All references cited herein are expressly incorporated by reference in their entirety.

What is claimed is:

1. An interstitial brachytherapy apparatus for delivering radioactive emissions to an internal body location comprising:

(a) a catheter body member having a proximal end and distal end;

(b) an inner spatial volume disposed proximate to the distal end of the catheter body member;

(c) an outer spatial volume defined by an expandable surface element disposed proximate to the distal end of the body member in a surrounding relation to the inner spatial volume; and

(d) a radiation source disposed in the inner spatial volume and generating a three-dimensional isodose profile that is substantially similar in shape to the expandable surface element.

2. The apparatus of claim **1**, wherein the inner and outer spatial volumes are configured to provide a minimum prescribed absorbed dose for delivering therapeutic effects to a target tissue, the target tissue being defined between the outer spatial volume expandable surface and a minimum distance outward from the outer spatial volume expandable surface, the apparatus providing a controlled dose at the outer spatial volume expandable surface to reduce or prevent necrosis in healthy tissue proximate to the expandable surface.

3. The apparatus of claim **2**, wherein a predetermined spacing is provided between said inner spatial volume and the expandable surface element.

4. The apparatus of claim **3**, wherein the expandable surface element is adapted to contact tissue surrounding a resected cavity and adapted to conform the tissue to the desired shape of the expandable surface element.

5. The apparatus of claim **2**, wherein the minimum prescribed absorbed dose is 40 Gray at a distance of at least one centimeter from the expandable surface element.

6. The apparatus of claim **5**, wherein the dose rate in at least a portion of the target tissue is between about 0.4 and 0.6 Gray/hour.

7. The apparatus of claim **5**, wherein the maximum absorbed dose delivered to the target tissue is less than 100 Gray.

8. The apparatus of claim **2**, wherein the outer spatial volume has a diameter between about two and four centimeters.

9. The apparatus of claim **2**, wherein the inner spatial volume is an inner closed, distensible chamber defined by a further radiation transparent wall.

10. The apparatus of claim **9**, wherein the radioactive source is in a fluid form.

11. The apparatus of claim **10**, wherein the expandable surface element is a solid distensible surface and the outer spatial volume is a closed, distensible chamber and the expandable surface element is a radiation transparent wall.

12. The apparatus of claim 11, wherein a burst strength of the distensible chamber defining the outer spatial volume is greater than a burst strength of the chamber defining the inner spatial volume.

13. The apparatus of claim 1, wherein the expandable surface element is an expandable cage.

14. The apparatus of claim 13, wherein the expandable cage comprises a shape memory material.

15. The apparatus of claim 14, wherein the expandable cage comprises nitinol.

16. The apparatus of claim 1, wherein the radiation source is a solid radiation source.

17. The apparatus of claim 1, wherein the radiation source is a plurality of solid radiation sources arranged to provide an isodose profile having a shape substantially similar to the shape of the outer spatial volume.

18. The apparatus of claim 2, wherein the prescribed absorbed dose is delivered to the target tissue in substantially three dimensions.

19. A method for treating a proliferating tissue disease using interstitial brachytherapy at an internal body location comprising:

(a) surgically creating access to the proliferating tissue in a patient;

(b) surgically resecting at least a portion of the proliferating tissue to create a resection cavity within body tissue;

(c) providing an interstitial brachytherapy apparatus for delivering radioactive emissions comprising:

(i) a catheter body member having a proximal end and distal end;

(ii) an inner spatial volume disposed proximate to the distal end of the catheter body member;

(iii) an outer spatial volume defined by an expandable surface element disposed proximate to the distal end of the body member in a surrounding relation to the inner spatial volume; and

(iv) a radiation source disposed in the inner spatial volume and generating a three-dimensional isodose profile that is substantially similar in shape to the expandable surface element;

(d) intraoperatively placing the interstitial brachytherapy apparatus into the resection cavity until a prescribed absorbed dose has been delivered to tissue surrounding the apparatus; and

(e) removing the interstitial brachytherapy apparatus.

20. The method of claim 19, further including placing the radioactive source into the interstitial brachytherapy apparatus after the step of placing the apparatus into the tumor resection cavity.

21. The method of claim 19, further including removing the radioactive source from the interstitial brachytherapy apparatus before the step of removing the apparatus.

22. The method of claim 19, wherein the proliferating tissue is a patient's brain.

23. The method of claim 19, wherein the proliferating tissue is a patient's breast.

24. The method of claim 19, further including configuring the inner and outer spatial volumes to provide a minimum prescribed absorbed dose for delivering therapeutic effects to a target tissue, the target tissue being defined between the outer spatial volume expandable surface and a minimum distance outward from the outer spatial volume expandable surface, the apparatus providing a controlled dose at the outer spatial volume expandable surface to reduce or prevent necrosis in healthy tissue proximate to the expandable surface.

25. The method of claim 24, further including providing a predetermined spacing between said inner spatial volume and the expandable surface element.

26. The method of claim 25, wherein the expandable surface element is adapted to contact tissue surrounding a resected cavity and adapted to conform the tissue to the desired shape of the expandable surface element.

27. The method of claim 24, wherein the minimum prescribed absorbed dose is 40 Gray at a distance of at least one centimeter from the expandable surface element.

28. The method of claim 27, wherein the dose rate in at least a portion of the target tissue is between about 0.4 and 0.6 Gray/hour.

29. The method of claim 27, wherein the maximum absorbed dose delivered to the target tissue is less than 100 Gray.

30. The method of claim 24, wherein the outer spatial volume has a diameter between about two and four centimeters.

31. The method of claim 24, wherein the step of configuring the inner and outer spatial volumes includes expanding the inner and outer spatial volumes.

32. A method for treating a proliferating tissue disease using interstitial brachytherapy at an internal body location comprising:

(a) surgically creating access to the proliferating tissue in a patient;

(b) surgically resecting at least a portion of the proliferating tissue to create a resection cavity within body tissue;

(c) providing an interstitial brachytherapy apparatus for delivering radioactive emissions comprising:

(i) a catheter body member having a proximal end and distal end;

(ii) an inner spatial volume disposed proximate to the distal end of the catheter body member;

(iii) an outer spatial volume defined by an expandable surface element disposed proximate to the distal end of the body member in a surrounding relation to the inner spatial volume; and

(iv) a radiation source disposed in the inner spatial volume;

(d) intraoperatively placing the interstitial brachytherapy apparatus into the resection cavity;

(e) configuring the inner and outer spatial volumes to provide a minimum prescribed absorbed dose for delivering therapeutic effects to a target tissue, the target tissue being defined between the outer spatial volume expandable surface and a minimum distance outward from the outer spatial volume expandable surface, the apparatus providing a controlled dose at the outer spatial volume expandable surface to reduce or prevent necrosis in healthy tissue proximate to the expandable surface; and

(f) removing the interstitial brachytherapy apparatus.

33. The method of claim 32, wherein the step of configuring the inner and outer spatial volumes includes expanding the inner and outer spatial volumes.

34. A method for treating a proliferating tissue disease using interstitial brachytherapy at an internal body location comprising:

(a) surgically creating access to the proliferating tissue in a patient;

(b) surgically resecting at least a portion of the proliferating tissue to create a resection cavity within body tissue;

(c) providing an interstitial brachytherapy apparatus for delivering radioactive emissions comprising:

(i) a catheter body member having a proximal end and distal end;

(ii) an inner spatial volume disposed proximate to the distal end of the catheter body member;

(iii) an outer spatial volume defined by an expandable surface element disposed proximate to the distal end of the body member in a surrounding relation to the inner spatial volume; and

(iv) a radiation source disposed in the inner spatial volume;

(d) intraoperatively placing the interstitial brachytherapy apparatus into the resection cavity;

(e) adapting the expandable surface element to contact tissue surrounding the resection cavity to conform the tissue to the desired shape of the expandable surface element;

(f) delivering a prescribed absorbed dose to tissue surrounding the apparatus; and

(g) removing the interstitial brachytherapy apparatus.

35. The method of claim **34**, wherein the step of adapting the expandable surface element includes expanding the outer surface volume.

36. An interstitial brachytherapy apparatus for delivering radioactive emissions to an internal body location comprising:

(a) a catheter body member having a proximal end and distal end;

(b) an inner spatial volume disposed proximate to the distal end of the catheter body member;

(c) an outer spatial volume defined by an expandable surface element disposed proximate to the distal end of the body member in a surrounding relation to the inner spatial volume; and

(d) a radiation source disposed in the inner spatial volume;

wherein the inner and outer spatial volumes are configured to provide a minimum prescribed absorbed dose for delivering therapeutic effects to a target tissue, the target tissue being defined between the outer spatial volume expandable surface and a minimum distance outward from the outer spatial volume expandable surface, the apparatus providing a controlled dose at the outer spatial volume expandable surface to reduce or prevent necrosis in healthy tissue proximate to the expandable surface.

* * * * *

Exhibit C

(12) **United States Patent**
Winkler et al.

(10) **Patent No.: US 6,482,142 B1**
(45) **Date of Patent: Nov. 19, 2002**

(54) **ASYMMETRIC RADIATION DOSING APPARATUS AND METHOD**

(75) Inventors: **Rance A. Winkler**, Atlanta; **Timothy J. Patrick**, Alpharetta, both of GA (US)

(73) Assignee: **Proxima Therapeutics, Inc.**, Alpharetta, GA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **09/464,727**

(22) Filed: **Dec. 16, 1999**

Related U.S. Application Data

(63) Continuation-in-part of application No. 09/293,524, filed on Apr. 15, 1999, which is a continuation-in-part of application No. 08/900,021, filed on Jul. 24, 1997, now Pat. No. 5,913,813.

(51) **Int. Cl.**[7] **A61N 5/00**
(52) **U.S. Cl.** **600/3**
(58) **Field of Search** 600/1–8

(56) **References Cited**

U.S. PATENT DOCUMENTS

4,706,652	A	11/1987	Horowitz	128/1.2
4,754,745	A	7/1988	Horowitz	128/1.2
5,422,926	A	6/1995	Smith et al.	378/121
5,562,594	A	10/1996	Weeks	600/3
5,724,400	A	3/1998	Swerdloff et al.	378/65
5,800,333	A	9/1998	Liprie	600/3
5,803,895	A	9/1998	Kronholz et al.	600/3
5,851,182	A	12/1998	Sahadevan	600/407
5,863,284	A	1/1999	Klein	600/3

FOREIGN PATENT DOCUMENTS

WO	WO 97/19723	6/1997	A61N/5/00

OTHER PUBLICATIONS

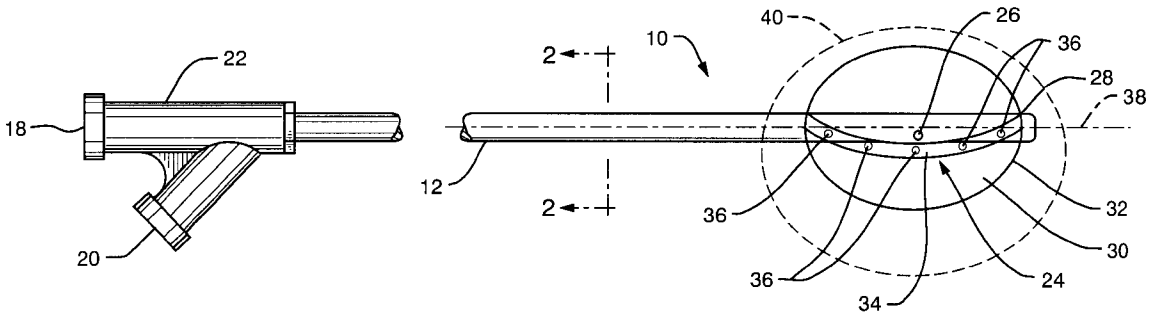
Ravinder, Nath, Ph.D. et al., Development of an ^{241} Am Applicator For Intracavitary Irradiation of Gynecologic Cancers, I.J. Radiation Oncology, Biology, Physics, May 1988, vol. 14, No. 5, pp. 969–978.

Primary Examiner—John P. Lacyk
(74) *Attorney, Agent, or Firm*—Thomas J. Engellenner; Ronald E. Cahill; Nutter McClennen & Fish LLP

(57) **ABSTRACT**

An interstitial brachytherapy apparatus of the invention delivers radioactive emissions in an asymmetric fashion to target tissue surrounding a surgical extraction site. The apparatus includes an expandable outer surface element defining an apparatus spatial volume, a radiation source disposed within the apparatus volume, and a means for providing predetermined asymmetric isodose curves within the target tissue. In one configuration, asymmetric isodose curves are created in the target tissue by shaping or locating the radiation source so as to be asymmetrically placed with respect to a longitudinal axis of the apparatus. In other configurations, asymmetric radiopaque shielding is provided between the radiation source and the target tissue. A surgical procedure using the apparatus is also described.

14 Claims, 4 Drawing Sheets



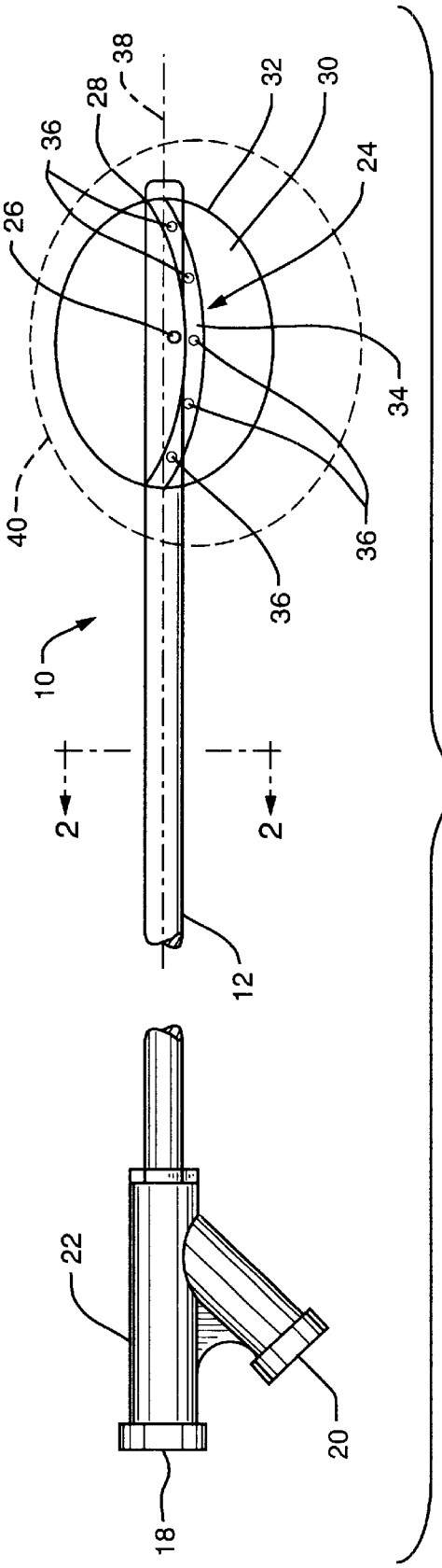


FIG. 1

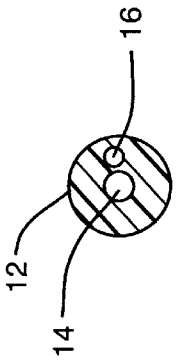


FIG. 2

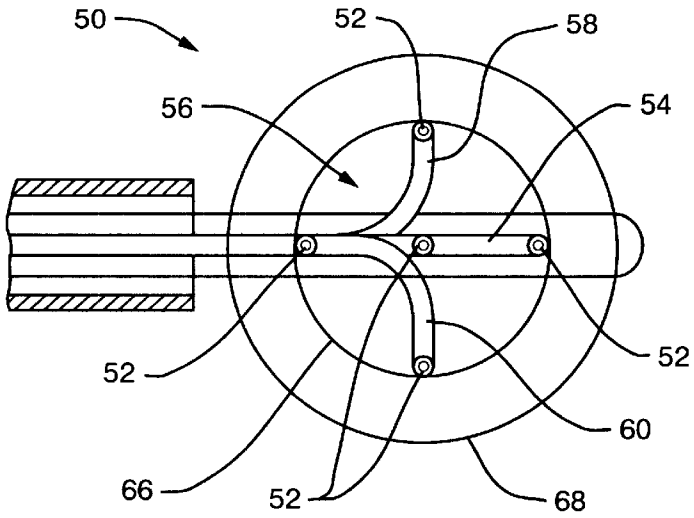


FIG. 3

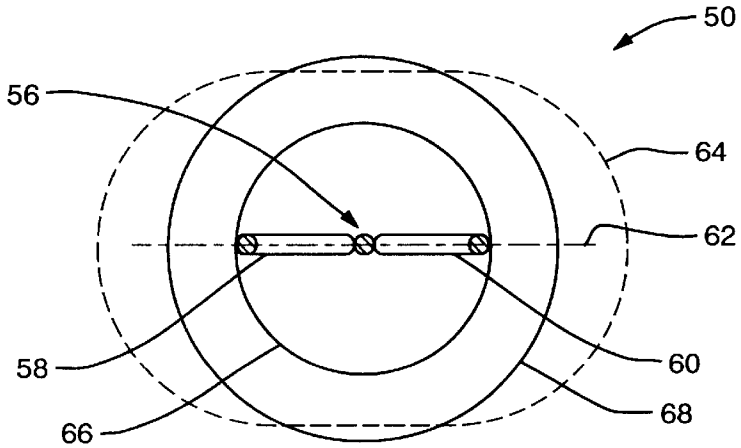


FIG. 3A

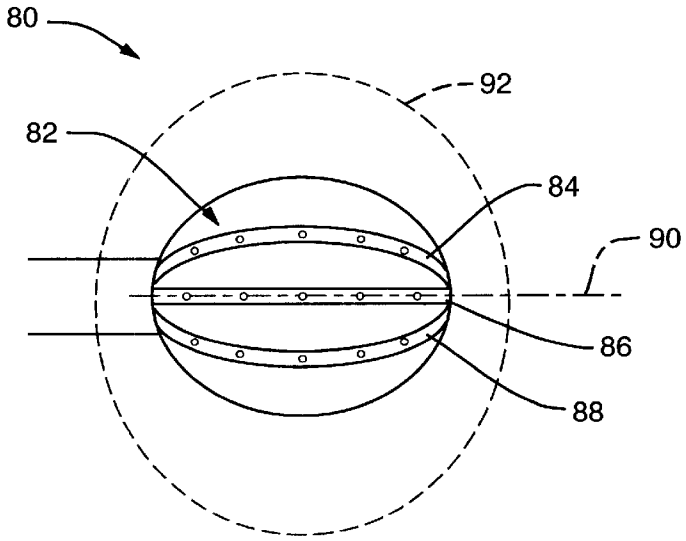


FIG. 4

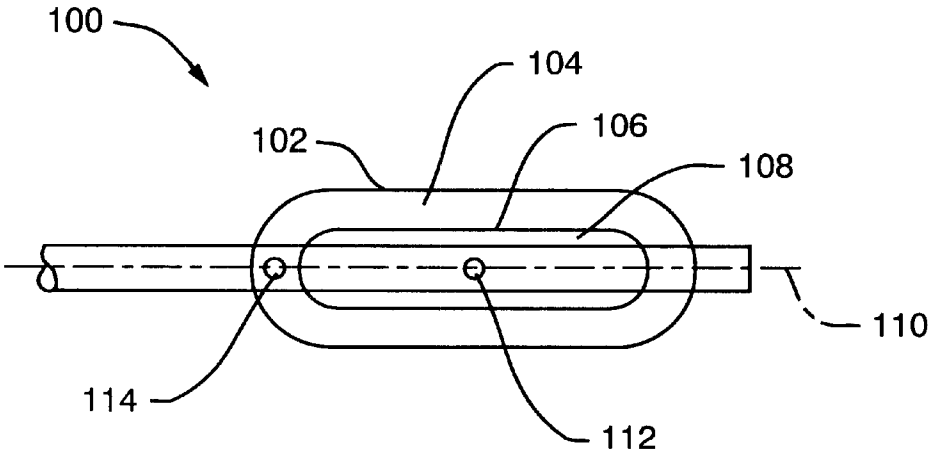

100
104
102
106
108
110
114
112

FIG. 5

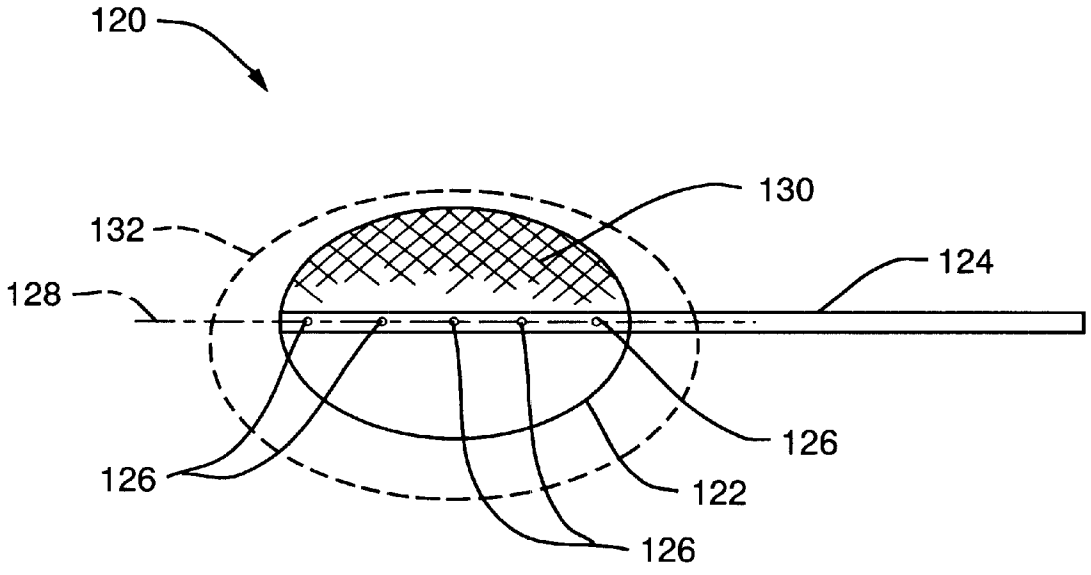

120
130
132
124
128
126
126
122
126

FIG. 6

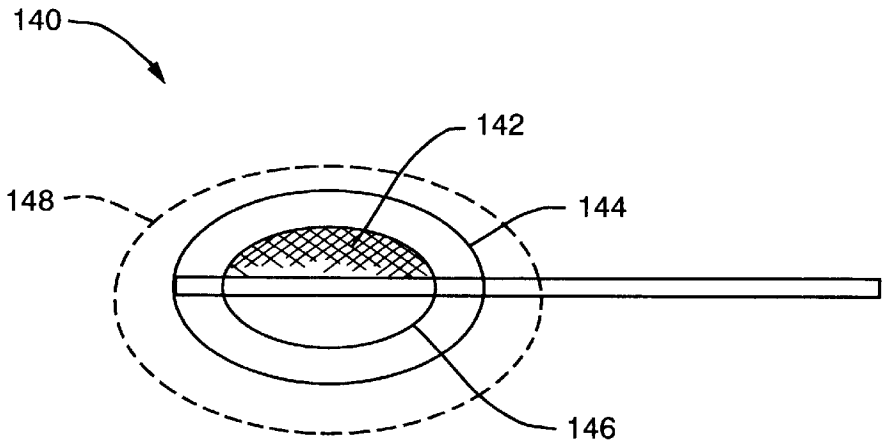


FIG. 7

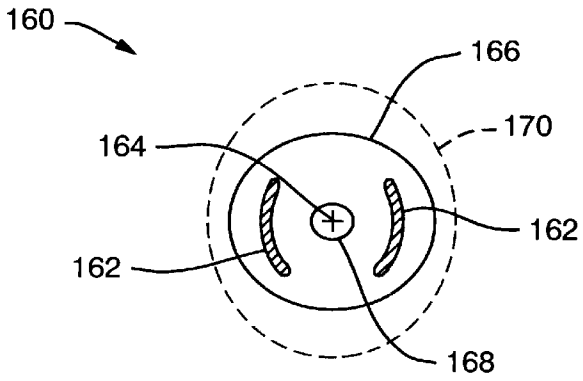


FIG. 8

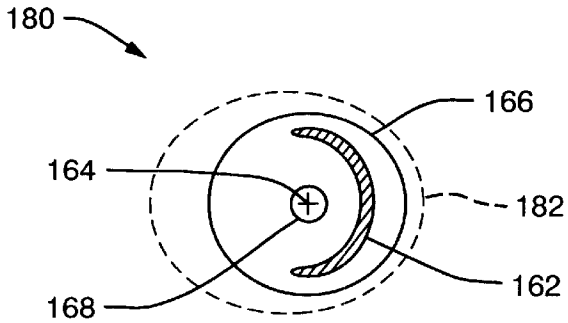


FIG. 9

ASYMMETRIC RADIATION DOSING APPARATUS AND METHOD

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation-in-part of co-pending U.S. patent application Ser. No. 09/293,524, filed Apr. 15, 1999, pending which is a continuation-in-part U.S. patent application Ser. No. 08/900,021, filed Jul. 24, 1997 (now issued as U.S. Pat. No. 5,913,813 to Williams et al.); the contents of these applications are specifically incorporated herein by reference.

BACKGROUND OF THE INVENTION

The, invention relates generally to an apparatus for use in treating proliferative tissue disorders, and more particularly to an apparatus for the treatment of such disorders in the body by the application of radiation.

Malignant tumors are often treated by surgical resection of the tumor to remove as much of the tumor as possible. Infiltration of the tumor cells into normal tissue surrounding the tumor, however, can limit the therapeutic value of surgical resection because the, infiltration can be difficult or impossible to treat surgically. Radiation therapy can be used to supplement surgical resection by targeting the residual tumor margin after resection, with the goal of reducing its size or stabilizing it. Radiation therapy can be administered through one of several methods, or a combination of methods, including external-beam radiation, stereotactic radiosurgery, and permanent or temporary interstitial brachytherapy. The term "brachytherapy," as used herein, refers to radiation therapy delivered by a spatially confined radioactive material inserted into the body at or near a tumor or other proliferative tissue disease site. Owing to the proximity of the radiation source, brachytherapy offers the advantage of delivering a more localized dose to the target tissue region.

For example, brachytherapy is performed by implanting radiation sources directly into the tissue to be treated. Brachytherapy is most appropriate where 1) malignant tumor regrowth occurs locally, within 2 or 3 cm of the original boundary of the primary tumor site; 2) radiation therapy is a proven treatment for controlling the growth of the malignant tumor; and 3) there is a radiation dose-response relationship for the malignant tumor, but the dose that can be given safely with conventional external beam radiotherapy is limited by the tolerance or normal tissue. In brachytherapy, radiation doses are highest in close proximity to the radiotherapeutic source, providing a high tumor dose while sparing surrounding normal tissue. Interstitial brachytherapy is useful for treating malignant brain and breast tumors, among others.

Interstitial brachytherapy is traditionally carried out using radioactive seeds such as ^{125}I seeds. These seeds, however, produce inhomogeneous dose distributions. In order to achieve a minimum prescribed dosage throughout a target region of tissue, high activity seeds must be used, resulting in very high doses being delivered in some regions in proximity to the seed or seeds which can cause radionecrosis in healthy tissue. One attempt to address this problem, at least with respect to limiting dosages to critical organs near the radioactive seed site, has been to provide a shield directly on a portion of the seed or on an applicator that holds the seed to shield the particularly sensitive tissue. (E.g., Nath et al., Development of an ^{241}Am Applicator for Intracavitary Irradiation of Gynecologic Cancers, *Intl. J. Radiation Oncology Biol. Phys.*, Vol., 14, pp. 969–978.) While this approach may be appropriate for some applications, it may still be overly "hot" for treating proximate tissue on the unshielded side of the seed, while not providing an effective dose on the shielded side of the seed.

Williams U.S. Pat. No. 5,429,582, entitled "Tumor Treatment," describes a method and apparatus for treating tissue surrounding a surgically excised tumor with radioactive emissions to kill any cancer cells that may be present in the tissue surrounding the excised tumor. In order to implement the radioactive emissions, Williams provides a catheter having an inflatable balloon at its distal end that defines a distensible reservoir. Following surgical removal of a tumor, the surgeon introduces the balloon catheter into the surgically created pocket left following removal of the tumor. The balloon is then inflated by injecting a fluid having one or more radionuclides into the distensible reservoir via a lumen in the catheter.

The apparatus described in Williams solves some of the problems found when using radioactive seeds for interstitial brachytherapy, but leaves some problems unresolved. The absorbed dose rate at a target point exterior to a radioactive source is inversely proportional to the square of the distance between the radiation source and the target point. s a result, where the radioactive source has sufficient activity to deliver a prescribed dose, say 2 centimeters into the target tissue, the tissue directly adjacent the wall of the distensible reservoir, where the distance to the radioactive source is very small, may still be overly "hot" to the point where healthy tissue necrosis may result. In general, the amount of radiation desired by the physician is a certain minimum amount that is delivered to a region up to about two centimeters away from the wall of the excised tumor. It is desirable to keep the radiation that is delivered to the tissue in the target treatment region within a narrow absorbed dose range to prevent over-exposure to tissue at or near the reservoir wall, while still delivering the minimum prescribed dose at the maximum prescribed distance from the reservoir wall. It is also desirable, at least in some applications, to provide these advantages while tailoring the radiation dosage to avoid fully dosing sensitive tissue or to reduce the amount of radiation that escapes the patient's body.

There its still a need for an instrument which can be used to deliver radiation from a radioactive source to target tissue within the human body with a desired intensity and at a predetermined distance from the radiation source without over-exposure of body tissues disposed between the radiation source and the target, and with the ability to shape the radiation dose to protect sensitive tissue or to protect against radiation exposure outside of the patient's body which may affect healthcare providers or others who might come close to the patient.

SUMMARY OF THE INVENTION

The present invention solves the problems described above by providing an interstitial brachytherapy apparatus for delivering radioactive emissions in an asymmnetric fashion to target tissue surrounding a surgical extraction site. The apparatus includes an expandable outer surface element defining an apparatus spatial volume, a radiation source disposed within the apparatus volume, and a means for providing predetermined asymmnetric isodose profile within the target tissue.

In one configuration, asymmetric isodose curves are created in the target tissue by shaping or locating the radiation source so as to be asymmetrically placed with respect to a

longitudinal axis of the apparatus. In one example of an apparatus having this configuration, an inner volume containing a liquid radioisotope is asymmetrically placed within the apparatus volume so as to result in an isodose profile in the target tissue that is asymmetric about the longitudinal axis of the apparatus.

In another example, the radiation source comprises a plurality of spaced apart solid radioactive particles disposed within the apparatus volume and arranged to provide a predetermined asymmetric isodose curve within the target tissue. In one particular example, the plurality of spaced apart radioactive particles are provided on a single elongate member that is shaped so that some of the radioactive particles are farther from the longitudinal axis of the apparatus than others. In other particular examples, a plurality of members carrying radioactive particles are provided with at least one of the members being shaped so as to place at least one radioactive particle asymmetrically with respect to the longitudinal axis of the apparatus.

An interstitial brachytherapy apparatus of the invention may also be implemented in a device having an expandable outer surface defining an apparatus volume, a radiation source disposed within and spaced apart from the expandable outer surface, and at least one asymmnetric radiation shield spaced apart from the radiation source, the asymmetric radiation shielding resulting in predetermined asymmetric isodose curves with in the target tissue. In one embodiment, radiopaque shielding is provided on a portion of the expandable outer surface. In another embodiment, the radiation source is encompassed within a second, inner surface within the apparatus volume, with radiopaque shielding provided on at least a portion of the inner surface. In still further embodiments, one or more radiation shields are spaced apart from the radiation source and within the apparatus volume to achieve the desired asymmetric isodose distribution within the target tissue.

The invention also provides a method for treating a proliferating tissue disease using interstitial brachytherapy at an internal body location. The method includes surgically creating access to the proliferating tissue within a patient and surgically resecting at least a portion of the proliferating tissue to create a resection cavity within body tissue. An interstitial brachytherapy apparatus for delivering radioactive emissions as described above is then provided and intra-operatively placed into the resection cavity. After a prescribed absorbed dose has been delivered to tissue surrounding the apparatus, the apparatus is removed. The radioactive source material may be placed into the interstitial brachytherapy apparatus after the apparatus is placed in the resection cavity, and may be removed before the apparatus is removed. The method has particular applications to brain and breast cancers.

DESCRIPTION OF THE DRAWINGS

The foregoing features, objects and advantages of the invention will become apparent to those skilled in the art from the following detailed description of a preferred embodiment, especially when considered in conjunction with the accompanying drawings in which:

FIG. **1** is a side view of an interstitial brachytherapy apparatus of the invention for delivering asymmetric radioactive doses to body tissue;

FIG. **2** is a cross-sectional view taken along the line **2**—**2** in FIG. **1**;

FIG. **3** is a side view of an additional embodiment of an interstitial brachytherapy apparatus of the invention;

FIG. **3**A is an end view of the interstitial brachytherapy apparatus of FIG. **3**;

FIG. **4** is a side view of an additional embodiment of an interstitial brachytherapy apparatus of the invention;

FIG. **5** is a side view of an interstitial brachytherapy apparatus of the invention configured for use with a liquid radiation source.

FIG. **6** is a side view of an interstitial brachytherapy device of the invention employing radiopaque coatings;

FIG. **7** is a side view of an interstitial brachytherapy device of the invention employing radiopaque coating and a liquid radiation source; and

FIGS. **8** and **9** are end views of interstitial brachytherapy devices of the invention employing radiopaque shields.

DESCRIPTION OF THE PREFERRED EMBODIMENT

A surgical instrument **10** for providing radiation treatment to proliferative tissue in a living patient is illustrated in FIG. **1**. Surgical instrument **10** includes a tubular body member **12** having first and second lumens **14** and **16** (FIG. **2**) extending from proximal ports **18** and **20** in a molded hub **22**. The first lumen **14** carries a radioactive source **24** and second lumen **16** communicates with inflation port **26** formed through the side wall of the tube **12**.

Affixed to the tubular body **12** proximate the distal end **28** thereof is an outer spatial volume **30** defined by an outer polymeric film barrier **32** that is appropriately spaced from the radioactive source **24**. Outer volume **30** encompasses inflation port **26**. With no limitation intended, the distensible polymeric film walls may comprise a biocompatible, radiation resistant polymer, such as silastic rubbers, polyurethanes, polyethylene, polypropylene, polyester, or PVC. The outer spatial volume **30** may be filled with air, saline or, alternatively, a radiation absorbing fluid, such as a contrast media used in angiography. Alternatively, the surface of outer volume **30** need not be a solid material. For example the surface of the outer volume **30** could be an expandable cage formed from a shape memory metal, such as nitinol, or a suitable plastic, such as an expandable polyethylene cage. Such a cage can be formed in the desired shape to conform to a particular isodose profile, contracted for delivery to the target site in vivo, then expanded to cause the tissue surrounding the surgically resected region to take the appropriate shape. The size of the outer spatial volume **30** generally will correspond approximately to the amount of tissue resected. For some applications, the size of the outer spatial volume **30** may be slightly smaller than the resected volume while for other applications, the outer spatial volume will be slightly larger than the resected volume, allowing the expandable surface of the outer spatial volume to urge tissue on the surface of the resected region into the appropriate shape to promote an even dose distribution around the outer spatial volume in the target tissue. In typical applications, the outer spatial volume has a diameter of approximately 2 to 6 centimeters.

Radiation source **24** comprises a wire **34** having one or more solid radioactive particles **36** located on the wire **34**. For example, radioactive micro spheres of the type available from the 3M Company of St. Paul, Minn., may be used as the solid radioactive particles. Such a solid radioactive particle configuration offers an advantage in that it allows a wider range of radionuclides than if one is limited to liquids. Solid radionuclides that could be used with the delivery device of the present invention are currently generally available as brachytherapy radiation sources. Examples of

radioactive materials which can be selected by a person of ordinary skills in the art for use with the present invention may be found in Tables 1 to 4 of PCT Publication WO 97/19723, which is hereby incorporated by reference.

The, radioactive source **24** can either be preloaded into the catheter at the time of manufacture, or loaded into the device after it has been implanted into the space formerly occupied by the excised tumor. If loaded after implantation, the solid radiation emitting material **36** can be inserted through lumen **14** on a wire **34**, for example using an afterloader (not shown).

Radiation source **24** has an asymmetric configuration with respect to a longitudinal axis **38** of the instrument **10**. That is, radiation source **24** is shaped so as to result in an isodose profile **40** that varies radially about the longitudinal axis **38**. More simply, the isodose profile **40** of FIG. **1** has a shorter radius from the longitudinal axis **38** on the top side of the instrument **10** as shown in FIG. **1** than on the bottom side. The asymmetrically shaped isodose curve **40** may be created by providing a plurality of solid radioactive particles **36** on a curved wire **34** in a spaced apart relationship. This configuration will result in certain of the solid radioactive particles **36** being farther from the longitudinal axis **38** of the instrument **10** than others, and will result in the illustrated asymmetric isodose profile **40**. One way to provide the illustrated radioactive source **24** configuration is to form wire **34** from a solid or tubular shape memory alloy such as nickel-titanium alloys known in the art to have such properties. Wire **34** can then be preformed to the desired shape, can be compressed into a substantially straight configuration to pass through lumen **14**, and will resume its desired shape once inside volume **30** where wire **34** will be free from steric constraints imposed inside the lumen **14**. The resulting asymmetric isodose curve **40** can be further tailored by using solid radioactive particles **36** having differing specific activities to achieve the desired dosing.

In,one embodiment, volume **30** and barrier **32** act to separate target tissue from the radiation source **24**. Ideally, radiation therapy should make use the inherent difference in radiosensitivity between the tumor and the adjacent normal tissues to destroy cancerous tissue while causing minimal disruption to surrounding normal tissues. At high doses of radiation, however, the percentage of exposed cells that survive treatment decreases with first-order kinetics in proportion to increasing radiation dose. With increasing cell death comes increasing risk of necrosis or tissue death in healthy tissue that is treated with a high dose of radiation. Accordingly, it is desirable to keep the maximum radiation dose delivered by the brachytherapy apparatus as low as possible while still delivering the desired therapeutic dose to the desired range of tissue. One method for achieving this result is to provide a "hotter" radiation source in a spaced apart relationship to the target tissue. In this way, because the intensity of the radiation emitted by a source drops with the square of the distance from the source, the effective dosage may be maintained below necrosis levels in target tissue closest to the interstitial brachytherapy apparatus while providing the required dosage to a greater depth into the target tissue. (See, e.g., U.S. Pat. No. 5,913,813 which is hereby incorporated by reference in its entirety.) The capability of the apparatus of the invention to deliver absorbed doses deeper into the target tissue than prior interstitial brachytherapy devices while controlling the dose in proximity to the apparatus to reduce or eliminate the risk of healthy tissue necrosis allows for the use of brachytherapy in a greater number of cases.

For example, it is desirable to provide an interstitial brachytherapy device configured to provide a dose in a therapeutic range, say between 40 to 60 Gray, at a distance between 0.5 and 1.0 cm from the outer spatial volume for an outer spatial volume having a diameter of 4.0 cm and being in contact with the resection cavity wall. In a typical embodiment, the radioactive source material ranges from approximately 150 to 450 mCi in activity and encompasses most of the target treatment area with a 0.4 to 0.6 Gray/hour isodose contour. At this treatment rate, treatment may be completed in approximately 3 to 7 days, or more commonly, in approximately 3 to 5 days.

In some applications, the desired dosing profile is consistent with the shape of the outer volume **30**. That is, the absorbed dose within the target tissue at points equidistant from the surface **32** of the outer spatial volume **30** should be substantially uniform in substantially every direction. Put another way, the three dimensional isodose profiles generated by the radiation source should be substantially similar in shape to the outer spatial volume **30**. Where the apparatus of the invention is deployed in soft tissue, it may also be important for the surface **32** of the outer spatial volume **30** to be sufficiently firm so as to force the target tissue to take on the shape of the surface **30** so that the desired relationship between the isodose profiles and the target tissue is achieved

While the interstitial brachytherapy device **10** of FIG. **1** may employ these techniques to positive effect, this device specifically alters the isodose profile for applications where particularly sensitive tissue or other concerns result in a desire to limit the dosage on one or more sides of the device as illustrated by isodose curve **40**.

In a further embodiment of the brachytherapy device **50** of the invention, illustrated in FIG. **3**, three solid radiation particles **52** are provided in a linear portion **54** of radiation source **56**, while two additional radiation particles **52** are provided on co-planar extending portions **58**, **60** of radiation source **56**. An end view of the device **50** of FIG. **3** is shown in FIG. **3**A with extending portions **58**, **60** provided in a single plane **62**, and resulting in isodose profile **64**. A second inner, expandable surface **66** can also be provided within outer surface **68**; the inner surface **66** enclosing the entirety of radiation source **56**.

By providing extending portions **58**, **60** having radioactive particles in the indicated co-planar relationship, areas of reduced dosage can be created on opposed sides of the device while maintaining symmetric dosing in all other directions. Of course, the number of sources and their configuration can be changed to create a desired asymmetric dosage. For example, an additional source could be added, for example above plane **62**, to result in a symmetric isodose profile in all directions except the direction below the plane **62** which would have a lower dosage.

An additional device **80** of the invention, shown in FIG. **4**, includes a radiation source **82** that is made up of three wires **84**, **86**, **88**, each having a plurality of solid radiation particles. Wire **86** is a straight wire extending along the longitudinal axis **90** of the device, while wires **84**, **88** each curve as wire **34** described above with respect to FIG. **1**. Wires **84**, **88** are coplanar, resulting in an isodose profile **92** that is similar to isodose profile **64** of FIG. **3**A. That is, the isodose profile will be symmetric in the plane in which the wires **84**, **88** are disposed, but will have areas of reduced dosage in directions transverse to that plane (i.e., in FIG. **4**, in the directions into and out of the page). As with the device **50** of FIGS. **3** and **3**A, device **80** can be configured with more or fewer wires **84**, **86**, **88**, and can be provided in configurations other than the depicted co-planar configuration in order to achieve desired asymmetric isodose profiles.

The asymmetric dosing effect achieved by the devices described above can also be achieved using a liquid radiation source. For example, device **100**, illustrated in FIG. **5**, has an outer surface **102** defining an outer volume **104** and an inner surface **106** defining an inner volume **108**. The inner surface **106** is asymmetrically shaped or located with respect to the longitudinal axis **110** of the device **100** so as to result in the desired asymmetric dosing when the inner volume **108** is filled with a radioactive fluid. The inner volume **108** is spaced apart from the outer surface **102** and can be filled with a material containing a predetermined radionuclide, for example, I-125, I-131, Yb-169 or other source of radiation, such as radionuclides that emit photons, beta particles, gamma radiation, or other therapeutic rays. The radioactive material contained within the inner volume **108** can be a fluid made from any solution of radionuclide(s), e.g., a solution of Ir-192, I-125 or I-131. A radioactive fluid can also be produced using a slurry of a suitable fluid containing small particles of solid radionuclides, such as Au-198, Y-90. Moreover, the radionuclide(s) can be embodied in a gel. One radioactive material useful in the invention is Iotrex™, a sterile single use, non-pyrogenic solution containing sodium 3-(^{125}I)iodo-4-hydroxybenzenesulfonate (^{125}I-HIBS), available from Proxima Therapeutics, Inc. of Alpharetta, Ga. The inner volume **108** may be filled with radioactive fluid through port **112**. Similarly, outer volume **104** can be filled on inflated using port **114**.

A desired asymmetric dosing profile having the dosing characteristics described above may also be created by using asymmetric shielding between the radiation source and the target tissue as illustrated in FIGS. **6** through **9**. In the device **120** of FIG. **6**, a balloon **122** is located on the distal end of catheter **124**. Radioactive particles **126** are disposed along the longitudinal axis **128** of the device. A portion of the surface, either inner or outer, of balloon **122** is coated with a radiopaque material **130** to result in asymmetric isodose curve **132**. Radiopaque materials suitable for coating onto a polymeric surface of balloon **122** include, for example, barium, tungsten, bismuth, tantalum and tin.

A further device **140** having radiopaque shielding **142** is illustrated in FIG. **7**. Device **140** includes an outer volume surface **144** and an inner volume surface **146**. Inner surface **146** may contain a liquid radiation source, or may enclose one or more solid particles as used in device **120** (FIG. **6**). In device **140**, the radiopaque material **142** is coated onto a portion of either the inner or outer side of the inner volume surface **146**, resulting in a desired asymmetric isodose profile **148**.

Additional devices **160**, **180** of the invention having radiation shielding **162** are illustrated in FIGS. **8** and **9**, respectively. In these devices **160**, **180**, one or more radiation shields **162** are provided between and spaced apart from a radiation source (not shown) located along a longitudinal axis **164** of the device and the target tissue, which will be located outside of expandable surface **166**. The radiation source can include a liquid or a solid radiation source as described above. Shields **162** can be formed from radiopaque materials including those described above with respect to the radiopaque coating and can extend longitudinally from a base on the device located within the expandable surface **166**.

As shown in FIG. **8**, device **160** has two radiation shields **162** on opposed sides of catheter **168**. This configuration results in lower radiation dosing on the two sides of the device **160** on which the shields **162** are located as shown by isodose curve **170**. Device **180** (FIG. **9**) has a single radiation shield **162** resulting in an asymmetric isodose curve **182** as shown. A person or ordinary skill in the art will recognize that other configurations may be employed to achieve desired isodose curves.

The interstitial brachytherapy apparatus of the invention can be used in the treatment of a variety of malignant tumors, and is especially useful for in the treatment of brain and breast tumors.

Many breast cancer patients are candidates for breast conservation surgery, also known as lumpectomy, a procedure that is generally performed on early stage, smaller tumors. Breast conservation surgery is typically followed by postoperative radiation therapy Studies report that 80% of breast cancer recurrences after conservation surgery occur near the original tumor site, strongly suggesting that a tumor bed "boost" of local radiation to administer a strong direct dose may be effective in killing any remaining cancer and preventing recurrence at the original site. The apparatus described herein can be used for either the primary or boost therapy. Numerous studies and clinical trials have established equivalence of survival for appropriate patients treated with conservation surgery plus radiation therapy compared to mastectomy.

Surgery and radiation therapy are also the standard treatments for malignant solid brain tumors. The goal of surgery is to remove as much of the tumor as possible without damaging vital brain tissue. The ability to remove the entire malignant tumor is limited by its tendency to infiltrate adjacent normal tissue. Partial removal reduces the amount of tumor to be treated by radiation therapy and, under some circumstances, helps to relieve symptoms by reducing pressure on the brain.

A method according to the invention for treating these and other malignancies begins by surgical resection of a tumor site to remove at least a portion of the cancerous tumor and create a resection cavity. Following tumor resection, but prior to closing the surgical site, the surgeon intraoperatively places an interstitial brachytherapy catheter apparatus, having an inner spatial volume and an outer spatial volume as described above but without having the radioactive source material loaded, into the tumor resection cavity. Once the patient has sufficiently recovered from the surgery, the interstitial brachytherapy catheter is loaded with a radiation source. The radioactive source dwells in the catheter until the prescribed dose of radiotherapy is delivered, typically for approximately a week or less. The radiation source is then retrieved and the catheter is removed. The radiation treatment may end upon removal of the brachytherapy apparatus, or the brachytherapy may be supplemented by further doses of radiation supplied externally.

It will be understood that the foregoing is only illustrative of the principles of the invention, and that various modifications can be made by those skilled in the art without departing from the scope and spirit of the invention, including, but not limited to, combinations of elements from different embodiments found herein. All references cited herein are expressly incorporated by reference in their entirety.

What is claimed is:

1. An interstitial brachytherapy apparatus for treating target tissue surrounding a surgical extraction comprising:

an expandable outer surface defining a three-dimensional apparatus volume configured to fill an interstitial void created by the surgical extraction of diseased tissue and define an inner boundary of the target tissue being treated;

a radiation source disposed completely within the expandable outer surface and located so as to be spaced apart from the apparatus volume, the radiation source further being asymmetrically located and arranged within the expandable surface to provide predetermined asymmetric isodose curves with respect to the apparatus volume.

2. A surgical apparatus for providing radiation treatment to target tissue comprising:

an expandable outer surface defining an apparatus volume;

a radiation source replaceably disposable within the expandable outer surface, the radiation source comprising a plurality of solid radiation sources arranged to provide predetermined asymmetric isodose curves within the target tissue, the plurality of solid radiation sources being provided in a spaced apart relationship on a single elongate member, the single elongate member being shaped to provide asymmetric placement of the spaced apart solid radiation sources with respect to a longitudinal axis through the apparatus volume.

3. The apparatus of claim **2**, further comprising a catheter in communication with the apparatus volume, the elongate member extending through the catheter into the apparatus volume.

4. The apparatus of claim **3**, wherein the elongate member is formed of a shape memory alloy, the elongate member being shaped to provide asymmetric placement of the spaced apart solid radiation sources, taking on a substantially straight shape while being inserted through the catheter to the apparatus volume, and resuming an asymmetric shape when extended into the apparatus volume.

5. A surgical apparatus for providing radiation treatment to target tissue comprising:

an expandable outer surface defining an apparatus volume;

a radiation source replaceably disposable within the expandable outer surface, the radiation source comprising a plurality of solid radiation sources arranged to provide predetermined asymmetric isodose curves within the target tissue, wherein at least one of the plurality of solid radiation sources has a different specific activity from at least one other solid radiation source.

6. A surgical apparatus for providing radiation treatment to target tissue comprising:

an expandable outer surface defining an apparatus volume;

a radiation source replaceably disposable within the expandable outer surface, the radiation source comprising a plurality of solid radiation sources arranged to provide predetermined asymmetric isodose curves within the target tissue, the plurality of radiation sources being provided on at least two elongate members extending into the apparatus volume, at least one of the elongate members being shaped to provide asymmetric placement of a radiation source with respect to a longitudinal axis through the apparatus volume.

7. The apparatus of claim **6**, wherein each of the at least two elongate members includes a plurality of solid radiation sources provided in a spaced apart relationship.

8. The apparatus of claim **1**, wherein the expandable outer surface is sufficiently rigid to deform the target tissue into the shape of the expandable outer surface, causing the predetermined asymmetric isodose curves to penetrate into the target tissue to a prescribed depth.

9. An interstitial brachytherapy apparatus for treating target tissue surrounding a surgical extraction comprising:

an expandable outer surface having a base and defining a three-dimensional apparatus volume configured to fill an interstitial void created by the surgical extraction of diseased tissue and define an inner boundary of the target tissue being treated;

a radiation source disposed completely within and spaced apart from the expandable outer surface; and

an asymmetric radiation shield spaced apart from the radiation source, the asymmetric radiation shield providing predetermined asymmetric isodose curves with respect to the apparatus volume.

10. The apparatus of claim **9**, wherein the asymmetric radiation shield comprises a radio-opaque material disposed on only a portion of the expandable outer surface.

11. The apparatus of claim **10**, wherein the expandable outer surface comprises an inflatable balloon.

12. The apparatus of claim **11**, wherein the radiation shield comprises a barium material disposed a portion of the inflatable balloon.

13. The apparatus of claim **9**, further comprising at least one radiation shield extending from the base of the expandable outer surface toward an opposite end of the expandable surface, the shield being in between and spaced apart from the radiation source and the expandable outer surface, the shield forming a radio-opaque barrier between a portion of the radiation source and the target tissue.

14. The apparatus of claim **13**, wherein the radiation shield comprises two shields provided on opposite sides of the radiation source.

* * * * *

Exhibit D

K071229

SENORX

MAY 18 2007

5. 510(K) SUMMARY

Prepared date	April 20, 2007
510(k) owner	**SenoRx, Inc.** 11 Columbia Aliso Viejo, CA 92656 P. 949.362.4800 F. 949.362.3200
Contact person	Eben Gordon
Device name	SenoRad Multi-Lumen Balloon Source Applicator for Brachytherapy
Common name	Multi-lumen balloon source applicator
Classification name	Remote controlled radionuclide source applicator
CFR classification	21 CFR 892.5700 90 JAQ
Predicate device	Adjustable Multi-Catheter Source Applicator (K062241) MammoSite Radiation Therapy System (K041929)
Decision date	11/9/2006 (K062241) 8/26/2004 (K041929)
Device description	The SenoRad applicator consists of a multi-lumen catheter connected to an inflatable spherical balloon that can be attached to commercially available High Dose Rate remote afterloader equipment for passage of the radiation source delivery wire. Five radiation source wire lumens are provided; one central lumen located along the long axis of the applicator and four curved lumens symmetrically offset from the central lumen. The balloon is inflated to a 4 or 5 cm spherical shape by a controlled volume injection of physiological saline to approximately 32 or 55 ml, respectively.
Indications for use	The SenoRad Multi-Lumen Balloon Source Applicator for Brachytherapy is intended to provide brachytherapy when the physician chooses to deliver intracavitary radiation to the surgical margins following lumpectomy for breast cancer.
Summary of substantial equivalence	Extensive preclinical testing was conducted to evaluate and characterize the performance of the SenoRad Multi-Lumen Balloon Source Applicator. Preclinical studies conducted included in vitro laboratory studies to demonstrate that the SenoRad applicator performed as intended under simulated use conditions. Biocompatibility testing was performed to

SENORX

demonstrate that the materials meet ISO 10993-1 requirements. The dosimetry of the SenoRad applicator was characterized. Based on these findings, it was concluded that the SenoRad applicator could deliver an equivalent radiation dose as the current brachytherapy applicators.

The SenoRad applicator has the following similarities to the previously cleared predicate devices: same indications for use; same intended use; same intended treatment site; same operating principle; same technological characteristics; equivalent dosimetric characteristics; and same sterilization method. The materials of construction vary in a manner that has no impact on device safety.

In summary, the SenoRad Multi-Lumen Balloon Source Applicator as described in this submission is substantially equivalent to the predicate devices.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
9200 Corporate Blvd.
Rockville MD 20850

MAY 18 2007

SenoRx, Inc.
% Mr. Mark Job
Responsible Third Party Official
Regulatory Technology Services LLC
1394 25th Street NW
BUFFALO MN 55313

Re: K071229
Trade/Device Name: SecoRad Multi-Lumen Ballon Source Applicator for Brachytherapy
Regulation Number: 21 CFR §892.5700
Regulation Name: Remote controlled radio-nuclide applicator system
Regulatory Class: II
Product Code: JAQ
Dated: May 2, 2007
Received: May 3, 2007

Dear Mr. Job:

We have reviewed your Section 510(k) premarket notification of intent to market the device referenced above and have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act) that do not require approval of a premarket approval application (PMA). You may, therefore, market the device, subject to the general controls provisions of the Act. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration.

If your device is classified (see above) into either class II (Special Controls) or class III (Premarket Approval), it may be subject to such additional controls. Existing major regulations affecting your device can be found in the Code of Federal Regulations, Title 21, Parts 800 to 898. In addition, FDA may publish further announcements concerning your device in the Federal Register.

Please be advised that FDA's issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the Act's requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Part 801); good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820); and if applicable, the electronic product radiation control provisions (Sections 531-542 of the Act); 21 CFR 1000-1050.

This letter will allow you to begin marketing your device as described in your Section 510(k) premarket notification. The FDA finding of substantial equivalence of your device to a legally marketed predicate device results in a classification for your device and thus, permits your device to proceed to the market.

If you desire specific advice for your device on our labeling regulation (21 CFR Part 801), please contact the Office of Compliance at one of the following numbers, based on the regulation number at the top of this letter:

21 CFR 876.xxx	(Gastroenterology/Renal/Urology	240-276-0115
21 CFR 884.xxx	(Obstetrics/Gynecology)	240-276-0115
21 CFR 894.xxx	(Radiology)	240-276-0120
Other		240-276-0100

Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21CFR Part 807.97). You may obtain other general information on your responsibilities under the Act from the Division of Small Manufacturers, International and Consumer Assistance at its toll-free number (800) 638-2041 or (240) 276-3150
or at its Internet address http://www.fda.gov/cdrh/industry/support/index.html.

Sincerely yours,

Nancy C Brogdon

Nancy C. Brogdon
Director, Division of Reproductive,
Abdominal, and Radiological Devices
Office of Device Evaluation
Center for Devices and Radiological Health

Enclosure

4. INDICATIONS FOR USE

510(k) Number (if known): K071229

Device Name: _____ SenoRad Multi-Lumen Balloon Source Applicator for Brachytherapy _____

Indications for Use:

The SenoRad Multi-Lumen Balloon Source Applicator for Brachytherapy is intended to provide brachytherapy when the physician chooses to deliver intracavitary radiation to the surgical margins following lumpectomy for breast cancer.

Prescription Use ___X____ AND/OR Over the Counter Use _____

(Part 21 CFR 801 Subpart D) (21 CFR 801 Subpart C)

(PLEASE DO NOT WRITE BELOW THIS LINE-CONTINUE ON ANOTHER PAGE OF NEEDED)

Concurrence of CDRH, Office of Device Evaluation (ODE)

Nancy C Brogdon

(Division Sign-Off)
Division of Reproductive, Abdominal, and Radiological Devices
510(k) Number K071229

Page __ of ___

Exhibit E

MAMMOSITE®

INSTRUCTION MANUAL

CYTYC

CYTYC SURGICAL PRODUCTS
301 E. Evelyn Avenue
Mountain View, CA 94041
PHONE (877) 668-2237 · FAX (650) 335-2714
www.mammosite.com

CAUTION: Federal (USA) law restricts this device to sale by or on the order of a physician.

CONTENTS

MammoSite® Applicator Tray

CAUTION: *Federal (USA) law restricts this device to sale by or on the order of a physician.*

Sterile: Sterilized with gamma radiation. Non-pyrogenic. Do not use if package is opened or damaged. Single use device.

SYMBOLS KEY

The following symbols may appear on the label or carton:

SYMBOL	DEFINITION
	Caution
	Use By Date (expiration date)
LOT	Lot Number
CE 0086	Quality System Certification
	Do Not Resterilize
	Do Not Reuse
	Non-pyrogenic

MammoSite Applicator Models

- **REF 2046**
  4 cm x 6 cm ellipsoidal
- **REF 2048**
  4 cm x 8 cm ellipsoidal
- **REF 2456**
  Variable 4 cm - 5 cm spherical
- **REF 2056**
  Variable 5 cm - 6 cm spherical

Accessory Components

(Supplied in individual non-sterile packages):

- **REF 9010**
  Varian HDR Afterloader Connectors with Obturators
- **REF 9011**
  Nucletron HDR Afterloader Connectors with Obturators
- **REF 9012**
  GammaMed® HDR Afterloader Connectors with Obturators

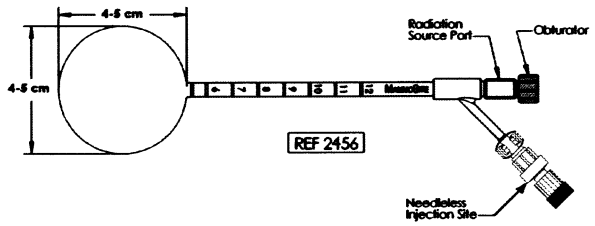
I. PRODUCT DESCRIPTION

The MammoSite applicator is used to position tissue and the radioactive source during breast brachytherapy treatments. It consists of a multi-lumen silicone catheter with an inflatible balloon assembly at its distal end. The MammoSite applicator is illustrated in Figures 1 and 2: A - D.

Figure 1. Illustration of MammoSite Applicator (deflated)

The MammoSite device is available in spherical 4-5 cm, spherical 5-6 cm, ellipsoidal 4 x 6 cm and ellipsoidal 4 x 8 cm sizes.

A.



B.

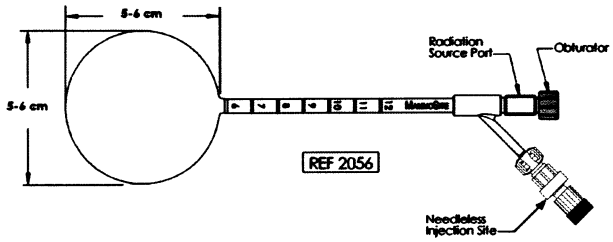
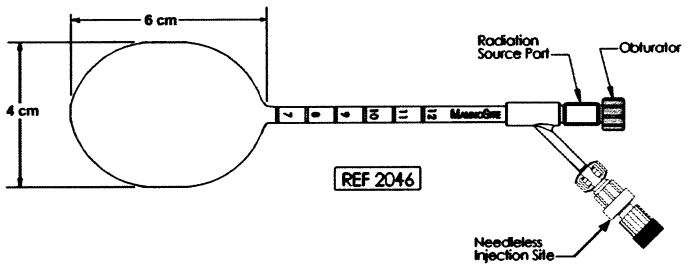


Figure 2: A and B. Illustration of MammoSite variable 4-5 cm and 5-6 cm spherical balloon (inflated).

C.



D.

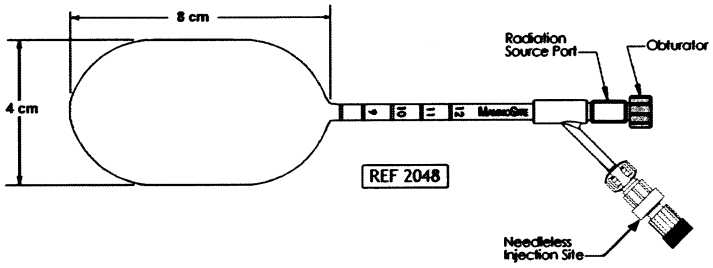


Figure 2: C & D Illustration of MammoSite 4 x 6 cm and 4 x 8 cm ellipsoidal balloon (inflated).

II. INTENDED USE/INDICATIONS

The MammoSite device is intended to provide brachytherapy when the physician chooses to deliver intracavitary radiation to the surgical margins following lumpectomy for breast cancer.

III. CONTRAINDICATIONS

- The MammoSite device should not be implanted if the shape and size of the resected tumor cavity is not consistent with the shape and size of the balloon and the fill volume ranges listed, per balloon size, in Table 10.
- Do not deliver radiation if the minimum distance from the balloon surface to the skin surface is less than 5 mm; or if the distance from the balloon surface to the skin surface is 5 mm over a continuous length greater than 1 cm on the surface of the skin.
- Do not implant the MammoSite device in patients with extreme or unusual anatomical features, e.g., extreme rib curves or very unequal amounts of breast tissue around lumpectomy cavity. This may cause the MammoSite applicator to become asymmetrical; thereby, affecting the conformal delivery of the radiation dose to the target tissue. Ensure the necessary balloon conformance prior to proceeding with radiation therapy.

IV. WARNINGS

The safety and effectiveness of the MammoSite RTS as a replacement for whole breast irradiation in the treatment of breast cancer has not been established.

- Never fill the system with more fluid than the maximum specified system volumes, per balloon size, listed in the *Instruction Manual* (Table 10). Overfilling of the balloon could result in rupture of the balloon and/or failure of the device.
- Do not use the MammoSite device if any leaks are observed and/or if the balloon does not resemble the approximate size and shape illustrated in Figure 2: A-D, per appropriate balloon size.
- Do not implant the MammoSite device if cavity is not visualized by breast imaging technique or if cavity is too small for the MammoSite balloon implantation. Imaging should verify a minimum distance of 5 mm from balloon surface to skin surface; however, a minimum distance of 7 mm from balloon surface to skin surface is recommended.

- Verify balloon placement and inflation using imaging prior to delivering each brachytherapy fraction. If balloon diameter changes greater than ten percent, re-evaluate treatment planning prior to delivering brachytherapy fraction.
- Altering patient position after CT may affect skin spacing, tissue to balloon conformance and dose distribution, which may result in an inappropriate patient treatment. Ensure analogous patient positioning from CT through delivery of all fractions.
- Verify treatment parameters per HDR manufacturer's instructions prior to proceeding with radiation therapy.
- Only medical personnel trained and authorized in the safe operation of HDR remote afterloaders should deliver brachytherapy using the MammoSite device.
- Do not use excessive force to implant or remove the MammoSite device. If the MammoSite applicator balloon or shaft becomes bound to the breast tissue, through tissue adhesion, the physician should consider surgical removal.
- For enhanced imaging purposes, the balloon may be filled with a sterile saline/contrast solution not to exceed the maximum fill volume ranges, per balloon size, listed in Table 10. For optimal balloon imaging and to minimize potential radiation dose attenuation, less than 10% contrast per fluid volume is recommended[1].
- For patients who have or may have an allergic reaction to iodinated materials, consider using non-ionic contrast agents.

V. PRECAUTIONS

- The MammoSite RTS should be used only by physicians trained in catheter placement, treatment planning, and radiation delivery prior to the use of the device.
- Keep catheter away from foreign materials at all times. Exercise extreme caution when handling the MammoSite balloon prior to and during implantation. Silicone materials are susceptible to damage by sharp objects/instruments and excessive pulling or pushing.
- Avoid contact of the product with glove talc, lint, particulate matter, soaps, oils, detergents or other surface contaminants. Caution should be used to avoid contamination of the MammoSite device.
- Store product at ambient temperature (20-25°C). Storage of product at high temperature and high humidity may damage the package.

[1] Kassas B, Mourtada F, Horton JL, and Lane RG. Contrast effects on dosimetry of a partial breast irradiation system. *Med Phys.*, 31: 1976-1979, 2004.

- Use syringes provided when inflating or deflating the MammoSite applicator. For proper inflation and deflation, ensure inflation lumen is not kinked or twisted.
- Exercise caution when handling the device to avoid excessive bending of the applicator shaft. Bending or coiling of the shaft to extreme angles could result in kinking of the radiation source pathway and/or failure of the device.
- To avoid possible contamination by foreign particulate do not remove obtura tor or stylet from radiation source port during device placement.
- Forceps should not be used during implantation of the balloon. Forceps can damage the balloon.
- During closure of the cavity, both deep and superficial, the balloon must be completely deflated and retracted out of the cavity to avoid needle puncture or abrasions which could lead to deflation of the balloon and/ or failure of the device.
- During all levels of closure, suture knots should be rotated away from the lumpectomy cavity to avoid puncture of the balloon by suture ends. When possible, place a layer of breast tissue between the balloon surface and the deepest line of suture to avoid suture abrasion on balloon which could lead to deflation of the balloon and/or failure of the device.
- Do not use surgical marking clips in conjunction with MammoSite device to avoid puncture of the device.
- The MammoSite RTS has only been tested using commercially available ^{192}Ir HDR sources. It is not recommended for use with HDR equipment other than those manufactured by Nucletron, Varian, or GammaMed®.
- Expose afterloader connectors to ambient conditions 72 hours prior to use or length modification.
- Ensure that the afterloader connector is fully seated within the radiation source port Luer connection of the applicator.
- If an incorrect connection is made to the fluid port rather than the radiation source port, fluid will flow out of the afterloader connector, indicating an incorrect connection. If undetected, fluid may backflow into the afterloader resulting in temporary operation suspension of the afterloader.
- Always replace Luer cap after accessing the needleless injection site to avoid contamination by foreign particulate and leakage from injection site. Needleless injection site should only be accessed for catheter inflation and deflation.
- In case of balloon deflation/rupture; carefully inspect the device upon removal to ensure that no fragments remain within the lumpectomy cavity.
- The afterloader connector pathway must be clear and patient movement minimized during radiation treatment to prevent kinking of the catheter.

VI. MAMMOSITE CLINICAL STUDY

A. 4 - 5 cm Spherical Balloon

DESIGN AND OBJECTIVE

A clinical study was conducted using the MammoSite variable 4-5 cm spherical balloon to demonstrate that the MammoSite RTS could be safely used to deliver a specific dose of radiation to the surgical margins following lumpectomy for breast cancer. The study objectives were to evaluate the performance of the MammoSite RTS applicator in patients with breast cancer, and in addition, to evaluate the safety of the MammoSite RTS in patients with breast cancer. This is an ongoing study in which enrollment has closed and the continued annual follow-up of patients is occurring. The protocol and average 35.8 month (1-54 month range) data are provided here to assist treating physicians in understanding the effects of using this device in patients to provide brachytherapy when choosing to deliver intracavitary radiation to the surgical margins following lumpectomy for breast cancer.

STUDY ENDPOINTS

The primary short-term safety endpoint was related to the applicator performance and its ability to deliver the specified treatment plan. This endpoint was defined as the ability of the applicator to deliver the final prescribed brachytherapy dose.

To demonstrate the short-term effects of the device, there are three key factors that were examined. These three factors are:

- The ability of the MammoSite device to be implanted and remain implanted throughout the duration of the radiation therapy.
- The ability of the balloon to inflate and maintain its integrity throughout the treatment as measured by the volume of fluid infused compared to the volume of fluid retrieved at the end of therapy and the ability of the MammoSite device to provide an unobstructed pathway for positioning of the radioactive source.

- The ability of the MammoSite applicator to be explanted without tissue damage that necessitates surgical reopening of the entry path to repair the damage.

The secondary safety endpoint was defined as the incidence rate of serious adverse events attributable to the MammoSite RTS that occur during the study. Data continues to be collected in order to understand the use of this device in lieu of external beam therapy. The data being collected includes an annual evaluation of the following: cosmetic evaluation (Harvard scale and digital photo), patient satisfaction, disease recurrence, systemic therapy, and adverse events.

PATIENT ENROLLMENT AND DEMOGRAPHICS

The study was designed to enroll at least 25 patients completing brachytherapy. A total of 70 patients were enrolled, 54 patients were implanted with the device, and a total of 43 patients completed brachytherapy. Eleven patients did not complete brachytherapy because of: cavity size being too small or too large (7), patient age (1), pathology (1), and inadequate skin spacing (2). Of the 43 that completed brachytherapy, 40 patients continue to be followed and 3 were lost to follow-up. Two patients died after receiving treatment with the device due to breast cancer metastasis. Neither patient had a local recurrence in the breast. One patient was diagnosed with Alzheimers and could not return for follow-up.

PATIENT SELECTION CRITERIA

The patient selection criteria was as follows:

INCLUSION CRITERIA

Patients selected to participate in this clinical investigation must:

- Be at least 45 years of age
- Be a T1, ≤ 2 cm, N0, M0 AJC Classification
- Should have a cavity size ≥3 cm in one dimension determined at the time of implant
- Have negative surgical margins (NSABP definition) after final surgery
- Applicator must be placed within ten weeks of the final lumpectomy surgery provided that ultrasound confirms the presence of a cavity just prior to implantation.

EXCLUSION CRITERIA

Patients selected to participate in this clinical investigation should not:

- Have a serious medical illness or condition that may effect the study or the use of the MammoSite applicator
- Be pregnant or breast-feeding (If appropriate, patient must use birth control during the study.)
- Have collagen-vascular disease
- Have extensive intraductal component (Harvard Definition, >25% DCIS)
- Have infiltrating lobular histology
- Have pure DCIS
- In addition, patients were excluded if the distance from cavity edge to skin surface was < 5mm.

PATIENT POPULATION DEMOGRAPHICS

The average age of the patients enrolled in the MammoSite study was 69 years. The majority of the patients (95%) were postmenopausal. The breast sizes treated in this study included A, B, C and D+ cup. The average tumor size was 1.07 cm. All patients enrolled in the study had T1, N0, and M0 staging. The patients' ER/PR and her2neu status were not collected and are not available.

BRACHYTHERAPY TREATMENT

All eligible patients received an HDR brachytherapy dose of 34 Gy to a 1 cm distance from the balloon surface, treating the lumpectomy cavity walls. This dose was fractionated over ten fractions, generally twice a day at least six hours apart. Each fraction lasted approximately 10-15 minutes, and the patients were able to go home between treatment fractions.

PATIENT FOLLOW-UP

For short-term efficacy, the primary endpoints were related to the applicator performance and its ability to deliver the specified treatment plan. All patients were followed at 24 hours, one week, and again one month after the completion of brachytherapy treatment. The protocol was subsequently amended to allow for the continued follow-up of the patients at least annually. Follow-up data ranging from 1 to 54 months post-treatment (mean 35.8 months) is provided here.

PATIENT ACCOUNTABILITY

Forty of the 43 treated patients are participating in the extended follow-up study. The average length of follow-up for these patients is 35.8 months with a range of 1 month to 54 months.

STUDY RESULTS

SHORT-TERM SAFETY: PRIMARY ENDPOINT RESULTS

Table 1

Device Performance and Endpoint Evaluation at Time of Treatment	
	N (%)
Number Enrolled	70
Number Evaluable	42*
Primary Endpoint	42 (100.0)
The ability of the MammoSite to be implanted and remain implanted throughout the duration of radiation therapy	42 (100.0)
The ability of the balloon to inflate and maintain its integrity throughout the treatment as measured by the volume of fluid infused compared to the volume of fluid retrieved at the end of therapy and the ability of the MammoSite to provide an unobstructed pathway for positioning of the radioactive source	42 (100.0)
The ability of the MammoSite applicator to be explanted without tissue damage that necessitates surgical reopening of the entry path to repair the damage	42 (100.0)
* One patient was enrolled, implanted, and completed brachytherapy. The patient met all study endpoints; however, was determined to be ineligible due to skin to balloon surface spacing distance and was therefore inevaluable.	

There were some instances of device malfunctions that occurred during the clinical study. See the Device Malfunctions section for complete details.

SHORT-TERM SAFETY: SECONDARY ENDPOINT RESULTS

There have been 10 serious events reported that occurred after device removal. For a complete description of these events, refer to the Adverse Events sections of the Instruction Manual.

OTHER STUDY RESULTS

At each follow-up visit, a cosmetic evaluation using the Harvard Scale was performed. The criteria was defined as follows:

Excellent	–	The treated breast looks essentially the same as the opposite breast.
Good	–	Mimimal but identifiable effects of radiation on the treated breast.
Fair	–	Significant effects of radiation on the treated breast.
Poor	–	Severe normal tissue sequelae secondary to irradiation

In addition, an ultrasound of the cavity was performed and the cavity healing was assessed by the study investigator using the following criteria:

Good	–	Seroma completely resolved, equal to, or smaller than previous ultrasound;
Fair	–	Seroma larger than previous ultrasound, however, patient is not symptomatic;
Poor	–	Seroma larger and patient is symptomatic.

Cosmetic results that were assessed by the study investigator are reported in Table 2.

Table 2

Harvard Scale[2]	Excellent/Good N (%)	Fair N (%)	Poor N (%)
At last follow-up (n=43)	39 (91%)	4 (9%)	0 (0%)
0 Mo- 12 Mo (n=43)	41 (95%)	2 (5%)	0 (0%)
13Mo-24Mo (n=36)	32 (89%)	4 (11%)	0 (0%)
25 Mo-36 Mo (n=34)	27 (79%)	7 (21%)	0 (0%)
37 Mo-48 Mo (n=24)	23 (96%)	1 (4%)	0 (0%)
>48 Mo (n=5)	4 (80%)	1 (20%)	0 (0%)

[2]Rose M, et al. Conservative surgery and radiation therapy for early stage breast cancer. long term cosmetic results. Arch. Surg. 124:153-157; 1989.

The results of the cavity healing assessment are shown in Table 3.

Table 3

Internal Cavity Healing			
Cavity Healing Scale	24 Hour (n = 26)	1 Week (n = 26)	1 Month (n = 26)
Good	19 (73%)	22 (85%)	17 (65%)
Fair	6 (23%)	3 (11%)	8 (31%)
Poor	0 (0%)	1 (4%)	0 (0%)
Not Reported	1 (4%)	0 (0%)	1 (4%)

ADVERSE EVENTS

The summary of the adverse events is provided in Table 4.

Table 4

Adverse Event Description	Patient Incidence N=43 N (%)
Erythema	31 (72.1%)
Catheter site drainage	24 (55.8%)
Breast pain	21 (48.8%)
Ecchymosis	15 (34.9%)
Breast fibrosis	14 (32.6%)
Telangiectasia	14 (32.6%)
Induration Breast	13 (30.2%)
Breast seroma	12 (27.9%)
Breast edema	12 (27.9%)
Dry desquamation	7 (16.3%)
Dry skin	7 (16.3%)
Skin discoloration	7 (16.3%)
Parasthesia	7 (16.3%)
Axillary pain	6 (14.0%)
Fatigue	5 (11.6%)
Pruritis	5 (11.6%)
Breast retraction	5 (11.6%)
Nausea	4 (9.3%)
Skin irritation	3 (7.0%)
Moist desquamation	3 (7.0%)
Hematoma	3 (7.0%)
Rash	3 (7.0%)
Asymptomatic fat necrosis	3 (7.0%)
Breast infection	2 (4.7%)
Blister/breast	2 (4.7%)
Lymphedema	2 (4.7%)

The following occur in less than 2% of the cases: Axillary infection, chronic inflammation, ulceration/breast, breast abscess, breast firmness, mastitis, vasodilation/lumpectomy, scar pain, skin thickening/ breast, eschar, incision firmness, embolus, abdominal pain, arm pain, hip pain, shoulder pain, chills, fever, accidental injury, dizziness, insomnia, anxiety, anorexia, colon carcinoma, dyspepsia, gastroenteritis, diagnostic test reaction, facial rash, hypoxia, skin carcinoma, pharyngitis, rhinitis, dry cough, asthma, arrhythmia, pallor, hypotension, bursitis, joint disorder/shoulder, arthralgia.

Summarized in Table 5 are the local tissue effects and their overall patient incidence and duration.

Table 5

	Patient Incidence Overall		Patient Incidence With Resolution		Resolution Duration (Days)		Patient Incidence Without Resolution	
	n=43		n=43				n=43	
Event	N	%	N	%	Mean	Range	N	%
Erythema	31	72.1	26	60.5	194	3-932	5	11.6
Catheter Site Drainage	24	55.8	24	55.8	6.5	0-48	0	0.0
Breast Pain	21	48.8	19	44.2	127.4	0-834	2	4.7
Ecchymosis	15	34.9	15	34.9	19.2	1-126	0	0.0
Breast Fibrosis	14	32.6	8	18.6	365.4	28-720	6	13.9
Telangiectasia	14	32.6	1	2.3	336.7	92-756	13	30.2
Induration	13	30.2	6	13.9	324.9	49-728	7	16.3
Breast Edema	12	27.9	12	27.9	162.6	2-581	0	0.0
Breast Seroma	12	27.9	12	27.9	204.7	0-504	0	0.0
Dry Desquamation	7	16.3	7	16.3	100.3	6-167	0	0.0
Dry Skin	7	16.3	7	16.3	232.9	9-668	0	0.0
Skin Discoloration	7	16.3	6	13.9	349.3	100-582	1	2.3
Pruritus	5	11.6	5	11.6	74.8	3-186	0	0.0
Breast Retraction	5	11.6	1	2.3	162	162-162	4	9.3
Asymptomatic Fat Necrosis	3	6.9	1	2.3	734	734-734	2	4.7
Hematoma	3	6.9	3	6.9	138	14-295	0	0.0
Moist Desquamation	3	6.9	3	6.9	16.3	10-28	0	0.0
Skin Irritation	3	6.9	3	6.9	106.3	61-137	0	0.0
Blister/breast	2	4.7	2	4.7	33.0	3-63	0	0.0
Breast Infection	2	4.7	2	4.7	112.6	36-189	0	0.0
Axillary Infection	1	2.3	1	2.3	12	12-12	0	0.0
Breast abscess	1	2.3	1	2.3	5	5-5	0	0.0
Breast firmness	1	2.3	1	2.3	267	267-267	0	0.0
Chronic Inflammation	1	2.3	1	2.3	110	110-110	0	0.0
Eschar	1	2.3	1	2.3	17	17-17	0	0.0
Incision Firmness	1	2.3	0	0.0	--	--	1	2.3
Mastitis	1	2.3	1	2.3	267	267-267	0	0.0
Scar Pain	1	2.3	1	2.3	266	266-266	0	0.0
Skin Thickening Breast	1	2.3	1	2.3	162	162-162	0	0.0
Ulceration Breast	1	2.3	1	2.3	185	185-185	0	0.0
Vasodilatation/Lumpectomy	1	2.3	1	2.3	140	140-140	0	0.0

Summarized in Table 6 are the late local tissue effects and their overall patient incidence that were reported 90 days after device removal. None of the events classified as related to the device were unanticipated.

Table 6

Adverse Event Description	Patient Incidence n=42	
	N	%
Telangiectasia	14	33.3
Induration	11	26.2
Breast Fibrosis	11	26.2
Breast Pain	9	21.4
Erythema	7	16.7
Breast Seroma	6	14.3
Breast Edema	6	14.3
Breast Retraction	5	11.9
Skin Discoloration	4	9.5
Asymptomatic Fat Necrosis	3	7.1
Hematoma	2	4.8
Chronic Inflammation	1	2.4
Skin Irritation	1	2.4
Dry Desquamation	1	2.4
Ulceration Breast	1	2.4
Breast Firmness	1	2.4
Dry Skin	1	2.4
Mastitis	1	2.4
Scar Pain	1	2.4
Skin Thickening Breast	1	2.4
Incision Firmness	1	2.4

There were ten serious events reported in the course of the study, all of which resolved. These events are summarized in Table 7.

Table 7

	Patient Incidence Overall
Serious Adverse Event	**N (%)**
Seroma	3 (7.0)
Abscess	1 (2.3)
Accidental injury	1 (2.3)
Colon Carcinoma	1 (2.3)
Embolus	1 (2.3)
Hypotension	1 (2.3)
Hypoxia	1 (2.3)
Breast Infection	1 (2.3)

DEVICE MALFUNCTIONS

There were fourteen device complications reported in the clinical study. None of these complications caused an adverse event. A description of the events is included in Table 8.

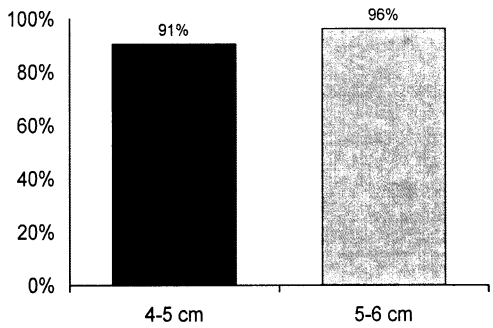
Table 8

Event	#	Description	Resolution
Balloon deflation	2	Surgical clips in cavity	Replaced MammoSite, Brachytherapy completed.
Balloon deflation	1	Needle Stick post implant.	Replaced MammoSite, Brachytherapy completed.
Balloon deflation	2	Needle Stick during implant.	Replaced MammoSite, Brachytherapy completed.
Balloon asymmetry	1	Pre-implant inflation test.	Replaced MammoSite, Brachytherapy completed.
Balloon asymmetry	3	Asymmetrical at the time of CT imaging.	MammoSite explanted. Patients received a different method of radiation therapy.
Balloon inflation Luer	1	Barbed Luer injection port slipped off the catheter.	Replaced MammoSite, Brachytherapy completed.
Balloon inflation Luer	1	Radiation source port was injected with saline.	Replaced MammoSite, Brachytherapy completed.
Fluid cap removed	1	Fluid port cap was removed. A loss of ~10 cc of fluid.	Fluid loss did not change the diameter. Patient's brachytherapy completed.
Source pathway kink	1	The source pathway became kinked during brachytherapy due to the patient's wound dressing.	The MammoSite was manipulated to resolve the kink and brachytherapy completed.
Tip of MammoSite pulled off	1	During the implantation, forceps broke the tip of the MammoSite as it was being implanted.	Replaced MammoSite, Brachytherapy completed.

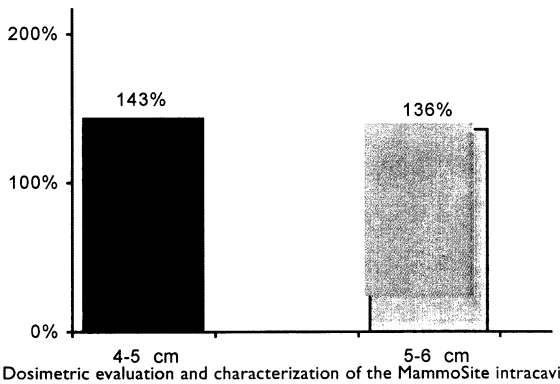
B. 5 - 6 cm Spherical Balloon

A clinical study was not conducted utilizing the 5-6 cm spherical MammoSite balloons; therefore, no clinical data is available demonstrating the outcome of patients using the 5-6 cm spherical balloon. The 5-6 cm MammoSite device was cleared based on dosimetry calculations. The following dosimetric characteristics for the 5-6 cm spherical device are substantially equivalent to the 4-5 cm spherical predicate device:

1) Coverage index[3] is a measure of the fraction of the breast prescription (target) volume receiving a dose equal to or greater than the prescribed dose.



2) Skin dose[3] is the dose to the skin at a minimum skin distance of 5 mm.

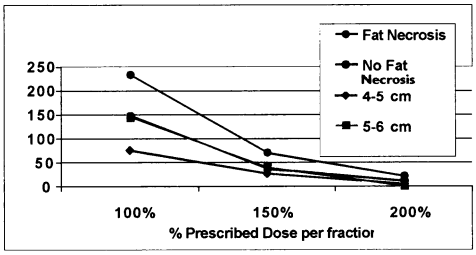


[3]Edmundson GK. Dosimetric evaluation and characterization of the MammoSite intracavitary breast brachytherapy device. Royal Oak (MI): Department of Radiation Oncology, William Beaumont Hospital; 1999.

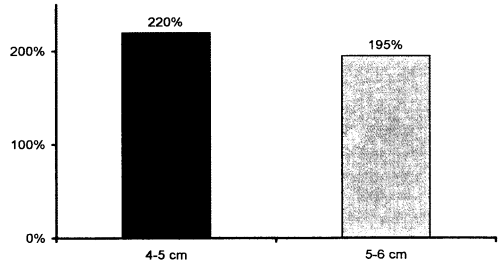
3) Hot spot comparison[4]: A hot spot is produced as a consequence of dose inhomogeneity within the treated volume of the breast and refers to volumes of tissue within the breast parenchyma that received excessive radiation dose, above what is prescribed by the treating physician. Symptomatic fat necrosis is a clinically significant toxicity that has been correlated with hot spots, specifically the volume of tissue receiving 150% of the prescribed dose (V150) and 200% of the prescribed dose (V200).

An analysis performed by Wazer demonstrates that there is a fairly distinct level at which fat necrosis is not observed. Plotting the data for the 5-6 cm MammoSite device on a graph with the Wazer data demonstrates that the V150 and V200 for the 5-6 cm MammoSite device falls below levels that were predictive of fat necrosis.

MammoSite device vs. Published Data



4) Dose gradient[3] relates to the dose on the surface of the balloon to the dose at the prescription depth and is a broad measurement of the dose inhomogeneity.



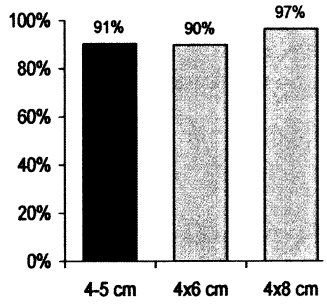
[3] Edmundson GK. Dosimetric evaluation and characterization of the MammoSite intracavitary breast brachytherapy device. Royal Oak (MI): Department of Radiation Oncology, William Beaumont Hospital; 1999.

[4] Wazer DE, Lowther D, Boyle T, et al. Clinically evident fat necrosis in women treated with high dose rate brachytherapy alone for early stage breast cancer. Int J Radiation Oncology, Biol Phys 50:107-111, 2001.

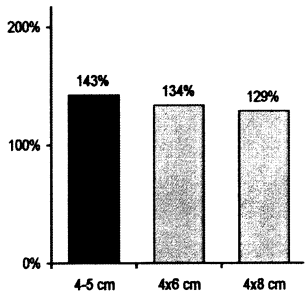
C. 4x6 and 4x8 cm Ellipsoidal Balloons

A clinical study was not conducted utilizing the ellipsoidal MammoSite balloons; therefore, no clinical data is available demonstrating the outcome of patients using the ellipsoidal shaped balloon. The ellipsoidal MammoSite device was cleared based on dosimetry calculations. The following dosimetric characteristics for the ellipsoidal shaped device are substantially equivalent to the 4-5 cm spherical predicate device:

1) Coverage index[3]



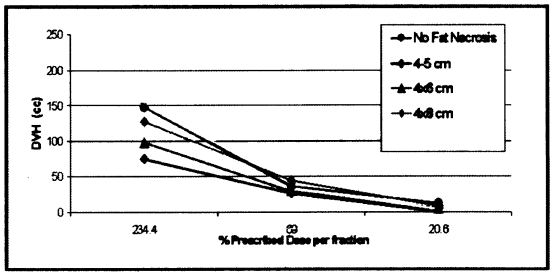
2) Skin dose[3]



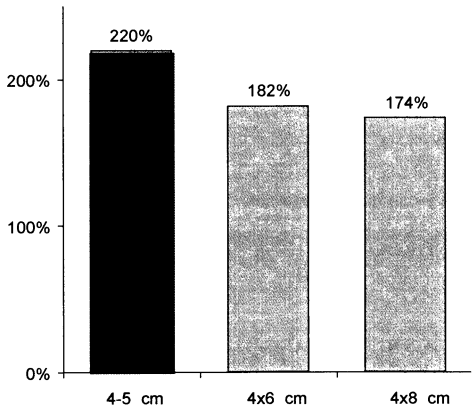
[3] Edmundson GK. Dosimetric evaluation and characterization of the MammoSite intracavitary breast brachytherapy device. Royal Oak (MI): Department of Radiation Oncology, William Beaumont Hospital; 1999.

3) Hot spot comparison[4]: An analysis performed by Wazer demonstrates that there is a fairly distinct level at which fat necrosis is not observed. Plotting the data for the ellipsoidal MammoSite devices on a graph with the Wazer data demonstrates that the V150 and V200 for the ellipsoidal MammoSite devices falls below levels that were predictive of fat necrosis.

MammoSite Device vs. Published Data



4) Dose gradient[3]



[3] Edmundson GK. Dosimetric evaluation and characterization of the MammoSite intracavitary breast brachytherapy device. Royal Oak (MI): Department of Radiation Oncology, William Beaumont Hospital; 1999.

[4] Wazer DE, Lowther D, Boyle T, et al. Clinically evident fat necrosis in women treated with high dose rate brachytherapy alone for early stage breast cancer. Int J Radiation Oncology, Biol Phys 50:107-111, 2001.

VII. PATIENT COUNSELING INFORMATION

The patient and/or her representative should be informed of the warnings, precautions and possible complications associated with the use of this product.

VIII. HOW SUPPLIED

CAUTION: Store product at ambient temperature (20-25°C). Storage of product at high temperature and high humidity may damage the package.

- The MammoSite Applicator Tray contains a MammoSite applicator, four 30 cc syringes, one 10 cc syringe, one trocar (8 mm diameter), one scalpel with #11 knife blade, one obturator, and one stylet. *Instruction Manual* and chart stickers are also provided.
- All MammoSite Applicator Trays are supplied in sterile packaging. Each package should be examined carefully prior to opening. Do not use the contents if there is any evidence of damage to the package or package seal that could compromise sterile integrity. Do not resterilize.
- Afterloader Connectors and additional obturators are packaged separately in individual non-sterile packages.

IX. DEVICE SPECIFICATIONS

The MammoSite applicator body is a multi-lumen extrusion of a silicone elastomer. The central lumen provides the radioactive source pathway. The source pathway's lumen diameter is sized to accommodate commercially available High Dose Rate (HDR) radioactive sources. The balloon assembly consists of a silicone balloon that inflates into either a spherical or ellipsoidal configuration based on the specified size of the inflated MammoSite balloon. The balloon fill volume ranges are listed, by MammoSite size/shape, in Table 10.

Graduation marks are printed on the applicator body to assist in placement of the applicator. The marks are measured at 1 cm intervals.

HDR Afterloader Connectors are available to enable connection to commercially available HDR remote afterloading systems.

I. MAMMOSITE DEVICE PLACEMENT PROCEDURE

The MammoSite device may be placed using a percutaneous technique up to ten weeks after lumpectomy. Proper patient selection must be determined by the physician. Patient selection criteria have been set forth by both surgical (American Society of Breast Surgeons) and radiation oncology (American Brachytherapy Society) professional organizations to guide in the appropriate selection of breast brachytherapy candidates[5,6]. Considerations include tumor type, size and histology, nodal status and patient age.

At the time of implant, balloon shape, size and fill volume that best approximates the cavity, should be identified. In addition, imaging should be performed as specified in Section II to confirm appropriate tissue to balloon conformance and adequate skin spacing.

A. MAMMOSITE BALLOON SELECTION

Prior to proceding with MammoSite device or placement, the appropriate balloon shape, size and fill volume range should be identified. The following guidelines provide direction for choosing appropriate balloon shape, size, and fill volume.

1. Identify the balloon shape that best approximates the shape of the cavity to be implanted.
   a. If length and width are approximately equal, choose a spherical MammoSite device.
   b. If the length is at least twice the width, choose an ellipsoidal MammoSite device.
2. Identify the balloon size that best approximates the size of the cavity to be implanted, allowing for inflation of the balloon to a volume greater than the cavity to maximize tissue to balloon conformance.
   a. If using a spherical MammoSite device, determine the cavity dimensions (L, W, & H). The minimum cavity diameter in at least one direction is 3 cm for the (4-5 cm) MammoSite balloon. The minimum cavity diameter in at least one direction is 4 cm for the (5-6 cm) MammoSite balloon.

[5] Arthur et. al. Accelerated partial breast irradiation: an updated report from the American Brachytherapy Society. *Brachytherapy*, 1:184-190,2003

[6] Consensus statement for accelerated partial breast irradiation. The American Society of Breast Surgeons. April 30, 2003.

b. If using an ellipsoidal MammoSite device, determine the cavity dimensions (L, W, & H). Choose device size in accordance with selection guide provided in Table 9 by multiplying L x W x H.

Table 9: Size Selection Guide

Size Selection Guide (L x W x H)*	Balloon Size
75 – 105	4 x 6 cm
106 – 130	4 x 8 cm

* L x W x H = # : This number will correspond to a range above, which will be used to determine balloon size.

3. Using Table 10, determine the balloon fill volume that is at least as large as and best fits the cavity to be implanted.

Table 10: Balloon Fill Volume

REF Number	Balloon Shape	Balloon Configuration	Balloon Fill Volume
2046	**Ellipsoidal**	**4 x 6 cm**	**60 – 65 cc**
2048	**Ellipsoidal**	**4 x 8 cm**	**75 – 80 cc**
2456	**Spherical**	**4 – 5 cm**	**35 – 70 cc**
2056	**Spherical**	**5 – 6 cm**	**70 – 125 cc**

B. SYSTEM VERIFICATION

Immediately prior to implantation of MammoSite device, complete the following procedure under sterile conditions.

WARNING: Never fill the system with more fluid than the maximum specified system volumes, per balloon size, listed in the *Instruction Manual* (Table 10). Overfilling of the balloon could result in rupture of the balloon and/or failure of the device.

WARNING: Do not use the MammoSite device if any leaks are observed and/or if the balloon does not resemble the approximate size and shape illustrated in Figure 2: A - D, per appropriate balloon size.

CAUTION: Use syringes provided when inflating or deflating the MammoSite applicator. For proper inflation and deflation, ensure inflation lumen is not kinked or twisted.

CAUTION: Exercise caution when handling the device to avoid excessive bending of the applicator shaft. Bending or coiling of the shaft to extreme angles could result in kinking of the radiation source pathway and/or failure of the device.

CAUTION: Keep catheter away from foreign materials at all times. Exercise extreme caution when handling the MammoSite balloon prior to and during implantation. Silicone materials are susceptible to damage by sharp objects/instruments and excessive pulling or pushing.

CAUTION: Avoid contact of the product with glove talc, lint, particulate matter, soaps, oils, detergents or other surface contaminants. Caution should be used to avoid contamination of the MammoSite device.

CAUTION: Always replace Luer cap after accessing the needleless injection site to avoid contamination by foreign particulate and leakage from injection site. Needleless injection site should only be accessed for catheter inflation and deflation.

1. Place catheter on a surgical instrument stand or other area clear of all surgical instrumentation.
2. Remove Luer cap on needleless injection site. Assemble the syringe to the applicator injection site and withdraw any air. Remove the syringe from the injection site while maintaining negative pressure.
3. Use Table 10 to identify the appropriate fluid fill volume range, per balloon size, and fill the syringe with normal sterile fluid solution. Do not exceed the maximum fill volume indicated.

4. Assemble the fluid-filled syringe to the injection site.
5. Slowly inject the sterile fluid solution into the applicator.
6. Repeat steps 3-5, as necessary, to fill the applicator balloon to its required fill volume.
7. Observe the balloon to ensure that it resembles the approximate size and shape illustrated in Figure 2: A-D.
8. While continuing to fully depress the syringe, check the balloon, applicator and injection site for any signs of leaks.
9. A small amount of air may be observed within the balloon. This is normal and will dissipate shortly.
10. Once it has been determined the MammoSite device is functioning properly, remove all of the fluid from the balloon by withdrawing the plunger of the syringe. Repeat as necessary to ensure all fluid is removed from applicator.

B. APPLICATOR PLACEMENT

The placement of the applicator may be accomplished through a variety of techniques. When implanting the ellipsoidal device, placement should not be perpendicular to the long axis of the cavity or at an angle to the cavity. Align the long axis of the catheter to the long axis of the cavity to maximize tissue to balloon conformance. Implantation techniques are at the discretion of the physician.

The following are descriptions of one surgical placement method and one post surgical placement method for the MammoSite applicator. For both placement methods, the obturator may be removed and replaced with the stylet for easier MammoSite insertion.

CONTRAINDICATION: The MammoSite device should not be implanted if the shape and size of the resected tumor cavity is not consistent with the shape and size of the balloon and the fill volume ranges listed, per balloon size, in Table 10.

CONTRAINDICATION: Do not implant the MammoSite device in patients with extreme or unusual anatomical features, e.g., extreme rib curves or very unequal amounts of breast tissue around lumpectomy cavity. This may cause the MammoSite applicator to become asymmetrical; thereby, affecting the conformal delivery of the radiation dose to the target tissue. Ensure the necessary tissue to balloon conformance prior to proceeding with radiation therapy.

WARNING: Never fill the system with more fluid than the maximum specified system volumes, per balloon size, listed in the *Instruction Manual* (Table 10). Overfilling of the balloon could result in rupture of the balloon and/or failure of the device.

WARNING: Do not use excessive force to implant or remove the MammoSite device. If the MammoSite applicator balloon or shaft becomes bound to the breast tissue, through tissue adhesion, the physician should consider surgical removal.

WARNING: For patients who have or may have an allergic reaction to iodinated materials, consider using non-ionic contrast agents.

CAUTION: Keep catheter away from foreign materials at all times. Exercise extreme caution when handling the MammoSite balloon prior to and during implantation. Silicone materials are susceptible to damage by sharp objects/instruments and excessive pulling or pushing.

CAUTION: Use syringes provided when inflating or deflating the MammoSite applicator. For proper inflation and deflation, ensure inflation lumen is not kinked or twisted.

CAUTION: Always replace Luer cap after accessing the needleless injection site to avoid contamination by foreign particulate and leakage from injection site. Needleless injection site should only be accessed for catheter inflation and deflation.

CAUTION: Exercise caution when handling the device to avoid excessive bending of the applicator shaft. Bending or coiling of the shaft to extreme angles could result in kinking of the radiation source pathway and/or failure of the device.

CAUTION: To avoid possible contamination by foreign particulate do not remove obturator or stylet from radiation source port during device placement.

CAUTION: Do not use surgical marking clips in conjunction with MammoSite balloon to avoid puncture of the device.

C.1 Surgical Placement (See Figure 3: A-D):

WARNING: Do not implant the MammoSite device if cavity is not visualized by breast imaging technique or if cavity is too small for MammoSite balloon implantation. Imaging should verify a minimum distance of 5 mm from balloon surface to skin surface; however, a minimum distance of 7 mm from balloon surface to skin surface is recommended.

WARNING: For enhanced imaging purposes, the balloon may be filled with a sterile saline/contrast solution not to exceed the maximum fill volume ranges, per balloon size, listed in Table 10. For optimal balloon imaging and to minimize potential radiation dose attenuation, less than 10% contrast per fluid volume is recommended.[1]

CAUTION: Forceps should not be used during implantation of the balloon. Forceps can damage the balloon.

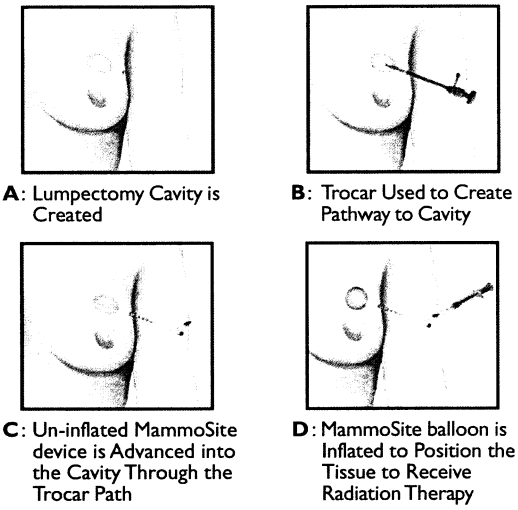
CAUTION: During closure of the cavity, both deep and superficial, the balloon must be completely deflated and retracted out of the cavity to avoid needle puncture or abrasions which could lead to deflation of the balloon and/or failure of the device.

CAUTION: During all levels of closure, suture knots should be rotated away from the lumpectomy cavity to avoid puncture of the balloon by suture ends. When possible, place a layer of breast tissue between the balloon surface and the deepest line of suture to avoid suture abrasion on balloon which could lead to deflation of the balloon and/or failure of the device.

[1] Kassas B, Mourtada F, Horton JL, and Lane RG. Contrast effects on dosimetry of a partial breast irradiation system. *Med Phys.*, 31: 1976-1979, 2004.

1. Place catheter on a surgical instrument stand or other area clear of all surgical instrumentation.
2. Choose an entry point away from the surgical incision (the physician should select a location for entry that provides the optimum pathway for the applicator/ balloon placement into the resected tumor cavity).
3. To create a pathway for device implantation, make a small nick in the skin using the knife blade included in the MammoSite Applicator Tray.
4. Through the skin nick, advance the trocar included in the MammoSite Applicator Tray into the surgical cavity.
5. Once the surgical cavity is penetrated, remove the trocar and advance the MammoSite applicator along the same trocar tract until the tip is touching the distal edge of the resected surgical cavity.
6. Inflate the balloon with sterile saline/contrast solution to the desired fill volume, per balloon size volumes listed in Table 10, to position the balloon in the re-sected tumor cavity. Syringes are provided to allow for solution delivery into the MammoSite balloon.
7. Fully deflate the balloon and retract out of the lumpectomy cavity prior to suturing to avoid balloon puncture or abrasion during closure.
8. Perform closure. It is recommended that suturing be done at a second level 1 cm or more below the surface. The additional line of suture will aid in obtaining the necessary distance between the balloon and the skin surface (>5 mm). This distance is important to minimize the potential for radiation skin effects. Complete closure using standard surgical suturing of the incision.
9. Position balloon in cavity and fully inflate the applicator with sterile saline/contrast solution to previously determined fill volume. Fluid fill volume may be ad-justed, per balloon size fill volume range (Table 10) to achieve desired cavity conformance and skin distance.
10. Recap needleless injection site with blue Luer cap provided.

Figure 3. Illustrations of MammoSite Device Placement



A: Lumpectomy Cavity is Created

B: Trocar Used to Create Pathway to Cavity

C: Un-inflated MammoSite device is Advanced into the Cavity Through the Trocar Path

D: MammoSite balloon is Inflated to Position the Tissue to Receive Radiation Therapy

11. If stylet has been used, remove and replace with obturator to prevent kinking of the applicator shaft between treatments.
12. Dress the applicator exit site. Avoid kinking the applicator shaft while dressing the site.
13. Record balloon fill volume on chart stickers provided in MammoSite applicator box and adhere to patient's chart.

C.2 Post Surgical Placement (See Figure 3: A-D):

WARNING: Do not implant MammoSite device if cavity is not visualized by breast imaging technique or if cavity is too small for MammoSite balloon implantation. Imaging should verify a minimum distance of 5 mm from balloon surface to skin surface; however, a minimum distance of 7 mm from balloon surface to skin surface is recommended.

WARNING: For enhanced imaging purposes, the balloon may be filled with a sterile saline/contrast solution not to exceed the maximum fill volume ranges, per balloon size, listed in Table 10. For optimal balloon imaging and to minimize potential radiation attenuation, less than 10% contrast per fluid volume is recommended.[1]

WARNING: For patients who have or may have an allergic reaction to iodinated materials, consider using non-ionic contrast agents

[1] Kassas B, Mourtada F, Horton JL, and Lane RG. Contrast effects on dosimetry of a partial breast irradiation system. *Med Phys.*, 31: 1976-1979, 2004.

1. Locate the lumpectomy cavity, using breast-imaging techniques, e.g., ultrasound.
2. Place catheter on a surgical instrument stand or other area clear of all surgical instrumentation.
3. Determine the entry point for insertion of the MammoSite device.
4. Administer local anesthesia to the trocar entry point and the planned applicator insertion pathway.
5. To create a pathway for device implantation, make a small nick in the skin using the knife blade included in the MammoSite Applicator Tray.
6. Through the skin nick, advance the trocar included in the MammoSite Applicator Tray into the surgical cavity.
7. Once the surgical cavity is penetrated, drain any fluids that have collected in the cavity.
8. Remove the trocar and advance the MammoSite device along the same trocar tract, using ultrasound guidance, until the tip of the applicator is touching the distal edge of the resected surgical cavity.
9. Inflate the balloon with sterile saline/contrast solution to the desired fill volume, per balloon size volumes listed in Table 10, to position the balloon in the resected tumor cavity and confirm applicator placement using ultrasound imaging. Syringes are provided to allow for solution delivery into the MammoSite balloon. Fluid fill volume may be adjusted per balloon size fill volume ranges (Table 10) to achieve desired cavity conformance and skin distance.
10. Recap needleless injection site with blue Luer cap provided.
11. If stylet has been used, remove and replace with obturator to prevent kinking of the applicator shaft between treatments.
12. Dress the applicator exit site. Avoid kinking the applicator shaft while dressing the site.
13. Record balloon fill volume on chart stickers provided in MammoSite applicator box and adhere to patient's chart.

II. RADIATION THERAPY DELIVERY

WARNING: Verify balloon placement and inflation using imaging prior to delivering each brachytherapy fraction. If balloon diameter changes by greater than ten percent, re-evaluate treatment planning prior to delivering brachytherapy fraction.

WARNING: Altering patient position after CT may affect skin spacing, tissue to balloon conformance and dose distribution, which may result in an inappropriate patient treatment. Ensure analogous patient positioning from CT through delivery of all fractions.

WARNING: Only medical personnel trained and authorized in the safe operation of HDR remote afterloaders should deliver brachytherapy using the MammoSite device.

WARNING: Verify treatment parameters per HDR manufacturer's instructions prior to proceeding with radiation therapy.

WARNING: For patients who have or may have an allergic reaction to iodinated materials, consider using non-ionic contrast agents

CAUTION: The MammoSite RTS has only been tested using commercially available ^{192}Ir HDR sources. It is not recommended for use with HDR equipment other than those manufactured by Nucletron, Varian or GammaMed.

CAUTION: Expose afterloader connectors to ambient conditions 72 hours prior to use or length modification.

CAUTION: Ensure that the afterloader connector is fully seated within the radiation source port Luer connection of the applicator.

CAUTION: If an incorrect connection is made to the fluid port rather than the radiation source port, fluid will flow out of the afterloader connector, indicating an incorrect connection. If undetected, fluid may backflow into the afterloader resulting in temporary operation suspension of the afterloader.

CAUTION: In case of balloon deflation/rupture, carefully inspect the device upon removal to ensure that no fragments remain within the lumpectomy cavity.

CAUTION: The afterloader connector pathway must be clear and patient movement minimized during radiation treatment to prevent kinking of the catheter.

ASSESSMENT OF BALLOON CONFORMANCE

- Prior to radiation therapy, conformance of the lumpectomy cavity to the balloon surface should be assessed using CT imaging. Ensure the necessary cavity to balloon conformance prior to proceeding with radiation therapy.
- Trained medical personnel should review these images. The conformance of the lumpectomy cavity walls to the balloon surface should be analyzed. The conformance of the lumpectomy cavity to the balloon surface should be at least 90% to allow for adequate radiation therapy coverage of the targeted treatment area.
- The MammoSite inflation volume may be adjusted to improve the conformance. If adequate conformance cannot be obtained, the MammoSite device should not be used for radiation therapy delivery.
- Dosimetry calculations have been made assuming the balloon takes the shape of an ellipsoid or sphere and therefore, the device should only be used in lumpectomy cavities that can be made to conform to the ellipsoidally or spherically shaped balloons.

The Radiation Oncologist develops a treatment plan designed to deliver a prescribed dose of radiation to the targeted treatment volume. Treatment planning is completed using commercially available planning software and should be based on the shape and inflated size of the implanted MammoSite balloon. Delivery of an optimized radiation dose is readily achievable with the spherical devices using a singular dwell position.

Delivery of an optimized radiation dose is readily achievable with the ellipsodial sizes using multiple dwell positions and times. Ensure that the isodose curves follow the inflated balloon's configuration or shape at the desired prescription point. Due to variable source positions and dwell times sample ellipsoidal treatment plans have been provided (See Figures 4a and b.)

Radiation therapy is delivered using a commercially available High Dose Rate (HDR) radiation source. When delivering radiation using High Dose Rate (HDR) remote afterloading, the MammoSite applicator connects to the HDR Remote Afterloader by attaching the red banded Luer end of the specified HDR Afterloader Connector to the red banded radiation source port of the MammoSite device, and the other end to the Afterloader's transfer/guide tube or indexer per manufacturer's instructions.

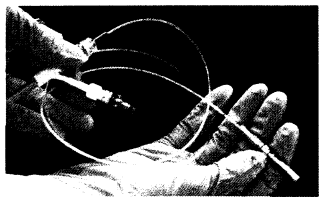
Table 11 below identifies the appropriate afterloader connector devices to be used in conjunction with each type of HDR afterloader. Both the MammoSite device and the appropriate afterloader connector are available through Cytyc Surgical Products. The transfer guide tube, quick connector or clamping adapter (accessory type is dependent on HDR afterloader model) are available through the HDR afterloader manufacturer. Contact the HDR afterloader manufacturer for information on the appropriate model number and instructions for use specific to each afterloader model.

Table 11

HDR Afterloader Model	Afterloader Connector (Cytyc Surgical Products Catalog. #)	Type of Transfer Guide Tube Required*	Type of Connector Required *
Varian – VariSource ID	REF 9010 – Varian HDR Afterloader Connectors	n/a	Standard VariSource D model quick connector
Varian – VariSource 200	REF 9010 – Varian HDR Afterloader Connectors	n/a	Standard VariSource 200 model quick connector
GammaMed - MammoSource	REF 9012 – GammaMed	n/a	Clamping adapter GMplus for 1.8 mm ø catheter
GammaMed*plus* / GammaMed*plus* 3/24	REF 9012 – GammaMed HDR Afterloader Connectors	n/a	Clamping adapter GMplus for 1.8 mm ø catheter
GammaMed12i(t)	REF 9012 – GammaMed HDR Afterloader Connectors	n/a	Clamping adapter for catheter ø 1.8 mm, GammaMed 12i(t)
Nucletron	REF 9011 – Nucletron HDR Afterloader Connectors	6F Flexible Implant Transfer Tube	Push-fit coupling

* Available through HDR manufacturer, not provided by Cytyc Surgical Products

Example of MammoSite afterloader connection to quick connector

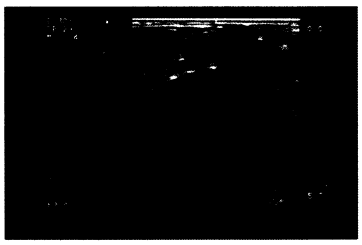


NOTE: The MammoSite device does not require special fixation to the tissue or skin to maintain its position within the lumpectomy cavity. The expansion of the MammoSite balloon fully fills the lumpectomy cavity. Perform the twice daily imaging using CT, x-ray or ultrasound to verify that the MammoSite device has not migrated.

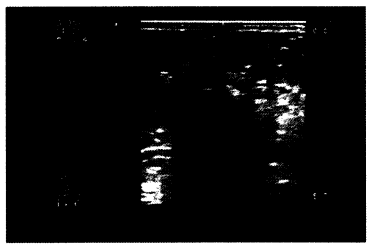
In addition, verify that the MammoSite positioning markers located on the catheter shaft are at the same depth. If it appears that the device has migrated, perform imaging to determine the exact positioning of the MammoSite device and refer to the Troubleshooting section.

The pre-clinical and clinical studies have shown that the spherical MammoSite device did not rotate within the cavity. Therefore, there is no need to assess rotation of the MammoSite device.

In addition to verifying that the MammoSite device/balloon has not migrated, use twice daily imaging (CT, X-ray or ultrasound) to verify that the balloon diameter has not changed. If balloon diameter changes by greater than 10%, re-evaluate treatment planning prior to delivering brachytherapy fraction. If it is determined that the balloon integrity has been compromised, refer to Troubleshooting Guidelines C1, Balloon Compromise. See images below.



Ultrasound image of inflated MammoSite Balloon



Ultrasound image of deflated MammoSite Balloon

Adhere to the HDR manufacturer's instructions concerning use of the radiation source. It is recommended that a test run be conducted prior to treatment to ensure the source is adequately positioned and functioning properly with the MammoSite applicator.

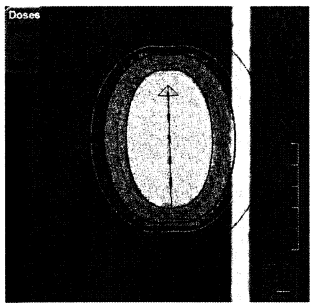
The MammoSite afterloader connectors may be cut to the appropriate length for use with various models of HDR remote afterloaders. Follow the remote afterloader manufacturer's recommendations for trimming and measuring the connectors and transfer tubes. Exposure to ambient conditions 72 hours prior to use or length modification is recommended to allow for any change in connector length due to temperature and humidity.

Timing of radiation therapy delivery (afterloading) is at the discretion of the physician, but should be planned so the therapy and applicator removal is complete within 29 days of MammoSite device placement.

Figure 4 - Treatment Planning- Ellipsoidal MammoSite Devices

4a) 4 cm x 6 cm ellipsoid

- Five HDR source dwell positions
- Weighted as follows:
  - Position 1 = 50%
  - Position 2 = 66%
  - Position 3 (at balloon center) = 100%
  - Position 4 = 66%
  - Position 5 = 50%
- Symmetric to balloon center
- 1.00 cm apart



4b) 4 cm x 8 cm ellipsoid

- Five HDR source dwell positions
- Equal times
- Symmetric to balloon center
- 1.25 cm apart
- Isodose surfaces closely match prescription volume

Note: Sample Treatment Plans are intended for generic guidance only and should not be used for primary dose calculation.

III. MammoSite® DEVICE REMOVAL PROCEDURE

WARNING: Do not use excessive force to remove the applicator. If the MammoSite applicator balloon or shaft material becomes bound to the breast tissue, through tissue adhesion, the physician should consider surgical removal.

Once the radiation therapy is completed, withdraw all fluid residing in the MammoSite balloon and carefully remove the applicator. Caution should be exercised when removing the MammoSite device from the resection cavity. Dispose of the MammoSite device as medical waste.

C. TROUBLESHOOTING GUIDELINES

Below are troubleshooting guidelines for potential device malfunctions. If any device malfunction is suspected, please call:

Cytyc Surgical Products • 1-877- 668-2237

I. Balloon Compromise

1) In the event of a suspected compromise of the balloon integrity, image the MammoSite device using CT. The size of the balloon should be noted.
2) In the event the balloon integrity has been compromised, the compromised MammoSite device may be removed and a new MammoSite device inserted.
3) The new MammoSite device may be inserted using the same pathway as the previous MammoSite device. Refer to Page 29, Section C.2 Post Surgical Placement, for complete instructions on implanting the MammoSite device.
4) The compromised MammoSite device should be returned to Cytyc Surgical Products for analysis.
5) CT imaging of the new MammoSite device should be performed to reassess treatment plan and conformance. Follow instructions in Section B.II.
6) Proceed with radiation therapy in accordance with the instructions in Section B.II.

II. MammoSite Shaft Kink

1) In the event of a kink in the catheter shaft, manually attempt to straighten the catheter shaft.
2) If unable to manually straighten the catheter shaft, use a stylet from the MammoSite Applicator Tray to open up or straighten the catheter shaft. The stylet should be inserted into the source pathway while manually straightening the catheter in the "kinked" section.
3) If the stylet does not open up or straighten the catheter shaft, deflate and replace the kinked MammoSite device with a new MammoSite device.
4) The new MammoSite device may be inserted using the same pathway as the previous MammoSite device. Refer to Page 29 Section C.2 Post Surgical Placement, for complete instructions on implanting the MammoSite device.

5) The kinked MammoSite device should be returned to Cytyc Surgical Products for analysis.
6) CT imaging of the new MammoSite device should be performed to reassess treatment plan and conformance. Follow instructions in Section B.II.
7) Proceed with radiation therapy in accordance with the instructions in Section B.II.

III. Obstruction of the Radiation Source Pathway

1) In the event of an obstruction in the MammoSite shaft, attach a dry syringe to the source pathway, pull a vacuum and attempt to draw out the obstruction.
2) If this does not move the obstruction, attempt to push the obstruction past the dwell position point using the syringe loaded with air or the stylet from the MammoSite Applicator Tray.
3) If the MammoSite device remains obstructed, remove and replace the MammoSite device.
4) The new MammoSite device may be inserted using the same pathway as the previous MammoSite device. Refer to Page 29, Section C.2 Post Surgical Placement, for complete instructions on implanting the MammoSite device.
5) The obstructed MammoSite device should be returned to Cytyc Surgical Products for analysis.
6) CT imaging of the new MammoSite device should be performed to reassess treatment plan and conformance. Follow instructions in Section B.II.
7) Proceed with radiation therapy in accordance with the instructions in Section B.II.

IV. Contamination of the Radiation Source Pathway

1) In the event that a contamination of the radiation source pathway is suspected, remove and replace the MammoSite device.
2) The new MammoSite device may be inserted using the same pathway as the previous MammoSite device. Refer to Page 29, Section C.2 Post Surgical Placement, for complete instructions on implanting the MammoSite device.
3) The contaminated MammoSite device should be returned to Cytyc Surgical Products for analysis.
4) CT imaging of the new MammoSite device should be performed to reassess treatment plan and conformance. Follow instructions in Section B.II.
5) Proceed with radiation therapy in accordance with the instructions in Section B.II.

V. MammoSite Device Dislodgement/Migration

1) In the event the MammoSite device dislodges or migrates out of the cavity, imaging should be performed. The imaging should be analyzed for the effect of the migration on the treatment plan and target volume.
2) If appropriate based on the imaging analysis, the device should be repositioned into its original position.
3) If it cannot be repositioned, remove and replace the MammoSite device.
4) The new MammoSite device may be inserted using the same pathway as the previous MammoSite device. Refer to Page 29, Section C.2 Post Surgical Placement, for complete instructions on implanting the MammoSite device.
5) The MammoSite device should be returned to Cytyc Surgical Products for analysis.
6) CT imaging of the new MammoSite device should be performed to reassess treatment plan and conformance. Follow instructions in Section B.II.
7) Proceed with radiation therapy in accordance with the instructions in Section B.II.

D. WARRANTY AND LIMITATIONS

Cytyc Surgical Products (Cytyc) warrants that each component of this system has been manufactured, packaged, and tested with reasonable care and shall be free from defects in workmanship and material when used in accordance with the instruction manual. Cytyc and its affiliates will not be liable for any incidental, special, or consequential loss, damage, or expense direct or indirect, from use of this system. Cytyc and its affiliates sole obligation shall be to repair or replace, at its option, any component of the system that we determine was defective at time of shipment if notice thereof is received within 1 year of shipment. Buyer assumes all liability, whether arising on warranty, contract, negligence, tort, or otherwise for damages resulting from the handling, possession, use, or misuse of the system by persons or entities other than Cytyc and its affiliates. Because Cytyc and its affiliates have no control over the operation, inspection, maintenance, or use of this system after sale and has no control over the selection of patients, THIS WARRANTY IS EXPRESSLY IN LIEU OF ANY OTHER EXPRESS OR IMPLIED WARRANTY OF MERCHANTABILITY OR FITNESS FOR ANY PARTICULAR PURPOSE, AND OF ANY OTHER OBLIGATION ON THE PART OF THE SELLER. The remedies set forth in the Warranty and Limitations shall be the exclusive remedy available to any person or entity. No agent, employee, or representative of Cytyc and its affiliates have any authority to change any of the foregoing or assume or bind Cytyc and its affiliates to any additional liability or responsibility in connection with this system.

CYTYC

CYTYC SURGICAL PRODUCTS
301 E. Evelyn Avenue
Mountain View, CA 94041
PHONE (877) 668-2237 · FAX (650) 335-2714
www.mammosite.com

719200 Rev. A

Exhibit F

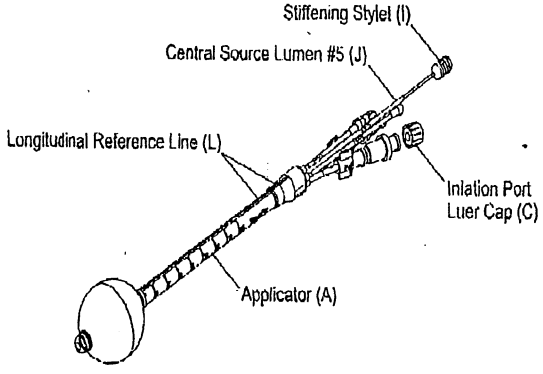


Figure 1: SENORX APPLICATOR

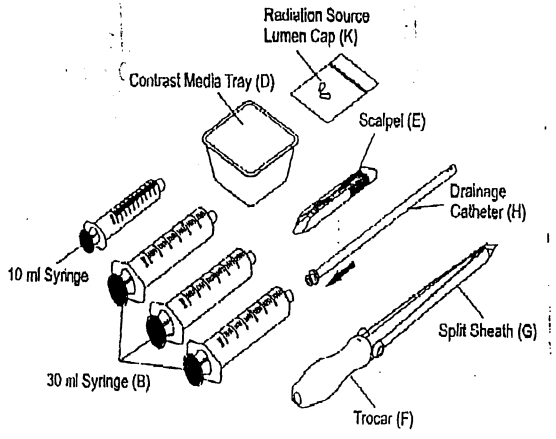


Figure 2: ACCESSORIES

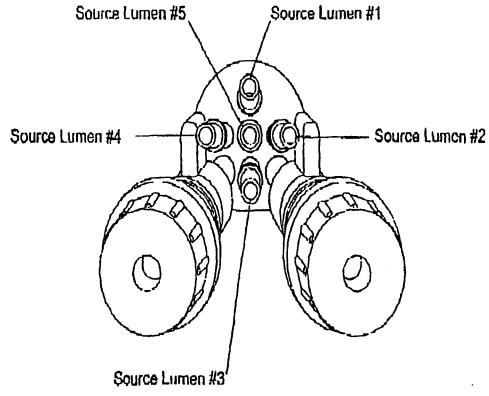


Figure 3: SOURCE WIRE LUMEN ORIENTATION

This product is covered by one or more of the following U.S. Patents: 6,923,754; 6,955,641; 7,241,178. Other domestic and foreign patents pending.

EXPLANATION OF SYMBOLS ON THE PACKAGE

REF	Catalogue Number
	Use by Date
LOT	Lot Number
CONT	Contents
STERILE R	Sterile (Gamma radiation)
	Attention, See Instructions for Use
	Do Not Reuse
	Upper Temperature Limit
	Keep away from sunlight
	Keep dry

SenoRx Inc.
Aliso Viejo, California
USA

SENORX

MULTI-LUMEN BALLOON SOURCE APPLICATOR FOR BRACHYTHERAPY

INSTRUCTIONS FOR USE

MODELS

B001-45
B011-45

IU0093 Rev. B
ECO 3776

SENORX

MULTI-LUMEN BALLOON SOURCE APPLICATOR FOR BRACHYTHERAPY

Caution: **Federal (USA) law restricts this device to sale by or on the order of a physician.**

DESCRIPTION

The SenoRx applicator consists of a multi-lumen catheter attached to an inflatable spherical balloon (Figure 1). Lumens are provided for attachment to commercially available HDR (High Dose Rate) remote afterloader equipment for passage of the radiation source delivery wire. Five radiation source wire lumens are provided; one central lumen located along the long axis of the applicator and four curved lumens symmetrically offset from the central lumen. A removable stiffening stylet is positioned in the central lumen. Two proximal ports are also provided with Luer-type connectors for balloon inflation/deflation and for application of intracavitary vacuum.

The SenoRx Multi-Lumen Balloon Accessories provided for introduction and deployment include: trocar with split sheath, drainage catheter, three, 30 ml and one, 10 ml inflation syringes, #11 scalpel, contrast media tray, radiation lumen caps and labels (Figure 2).

The SenoRx applicator model B001-45 is recommended for use with VariSource and Nucletron HDR afterloader equipment while model B011-45 is recommended for use with GammaMed afterloaders.

Warning: The safety and effectiveness of the SenoRx Applicator as a replacement for whole breast irradiation in the treatment of breast cancer has not been established.

INDICATIONS FOR USE

The SenoRx Multi-Lumen Balloon is intended to provide brachytherapy when the physician chooses to deliver intracavitary radiation to the surgical margins following lumpectomy for breast cancer.

CONTRAINDICATIONS

- The applicator is not intended for use in cavities that are too small, too large and/or of shapes unable to conform to an approximately spherical, 4 to 5 cm diameter SenoRx balloon.
- The applicator is not intended for use in patients with unusual anatomy including a highly curved rib structure and/or unequal amounts of tissue surrounding the cavity that may cause the SenoRx balloon to be asymmetrical.

WARNINGS

- Use caution when positioning the trocar tip near the chest wall or skin margin to avoid unintended tissue damage.
- Do not fill the Applicator with more than 58 ml of fluid as overfilling may result in balloon rupture and/or device failure.
- The Applicator must be pre-tested before implantation. Do not use the balloon if it is not approximately spherical and/or any leakage is detected.

- The breast cavity must be imaged before implantation to insure the applicator will fit appropriately. Do not use if the cavity is too small or if a skin surface to balloon surface distance of less than 5 mm will result.
- To insure appropriate treatment dose distribution, the SenoRx balloon must be imaged prior to delivering each fraction of radiation to confirm correct position, volume, skin spacing and conformance.
- If excessive resistance is encountered when attempting to remove the SenoRx applicator from the patient, surgical removal is recommended.
- Contrast media concentrations of less than 10% are recommended to prevent dose attenuation.
- Non-ionic contrast media is recommended for patients who are allergic to iodine-based agents.

PRECAUTIONS

- The SenoRx applicator must be used only by physicians trained in catheter implantation, radiation treatment planning and delivery.
- Metal vascular and marking clips should not be used during the lumpectomy procedure to prevent potential abrasion or puncture of the SenoRx™ balloon. Care should also be taken to direct suture knots and tails away from the cavity and whenever possible position tissue between the potential balloon surface and the tails.
- Store the SenoRx applicator at room temperature (20 to 25°C).
- Care must be taken when handling and manipulating the SenoRx balloon to prevent damage and foreign material contamination of the balloon surface.
- A scalpel should be used to incise the skin prior to inserting the trocar tip.
- Do not inject fluids into the Vacuum Port.
- Replace Luer caps and radiation lumen caps after use.
- Only clinical personnel trained in the operation of HDR afterloaders should deliver radiation using the SenoRx applicator.
- Verify that the appropriate afterloader connectors are available and function with the SenoRx applicator prior to treatment.
- Be sure that the SenoRx applicator is as straight as possible and free of sharp bends and kinks prior to connecting to the HDR afterloader.
- Inspect package before use. Discard if seal is compromised or packaging is damaged.

COMPLICATIONS

Complications that may be associated with the use of the SenoRx applicator are the same as those associated with the use of similar devices. These may include: erythema, catheter site drainage, breast pain, ecchymosis, breast fibrosis, telangiectasia, breast induration, breast seroma, breast edema, dry desquamation, dry skin, skin discoloration, parasthesia, axillary pain, fatigue, pruritis, breast retraction, nausea, skin irritation, moist desquamation, hematoma, rash, asymptomatic fat necrosis, breast infection, breast blister and lymphedema.

HOW SUPPLIED

The SenoRx applicator and accessories are provided sterile and are intended for single patient use only.

DIRECTIONS FOR USE

- PLACEMENT - Refer to Figures 1 & 2

1. Use ultrasound to identify the lumpectomy cavity.
2. Open the SenoRx applicator sterile package and remove the Applicator (A) and one 30 ml Syringe (B). Remove the Inflation Port Luer Cap (C) and inject 58 ml of sterile saline into the Applicator and inspect for leaks and spherical symmetry. Discard Applicator if defective. Withdraw saline from balloon.
3. Prepare a maximum 10% contrast media/sterile saline solution in the Tray (D) provided.
4. Determine the desired point on the breast surface for the insertion of the SenoRx applicator. Inject appropriate anesthetic to the skin and pathway to the lumpectomy cavity. Make a skin incision with the scalpel at the insertion point of sufficient length to fully insert the Trocar (F) tip. Dilate the skin incision, if desired. Advance the Trocar with Split Sheath (G) into the cavity. Remove the Trocar.
5. Attach a 30 ml syringe to the Drainage Catheter (H) and drain any fluids within the cavity by inserting the Drainage Catheter through the Split Sheath and suctioning. Remove the Drainage Catheter.
6. Insert the Applicator through the Split Sheath into the cavity. Remove the Sheath.
7. Remove the stiffening Stylet (I) from the Central Source Lumen (J). Attach a red radiation source lumen Cap (K).
8. Using the syringes provided, inflate the Applicator balloon with the contrast media solution to the desired fill volume.

Desired balloon diameter	Approximate balloon fill volume
4 cm	33 ml
5 cm	58 ml

9. Replace the Luer Cap on to the Inflation Port.
10. Use ultrasound to confirm appropriate placement, volume and cavity conformance. Fluid and air surrounding the Applicator balloon may be aspirated with a 30 ml Syringe attached to the Vacuum Port (L). The volume of the balloon may be adjusted through the Inflation Port (C). Replace Luer Caps when finished.
11. Apply a surgical dressing to the exit site with the catheter positioned to minimize bending.
12. Record the final balloon fill volume on the Labels provided and attach to the patient's chart.

- RADIATION DELIVERY - Refer to Figure 3

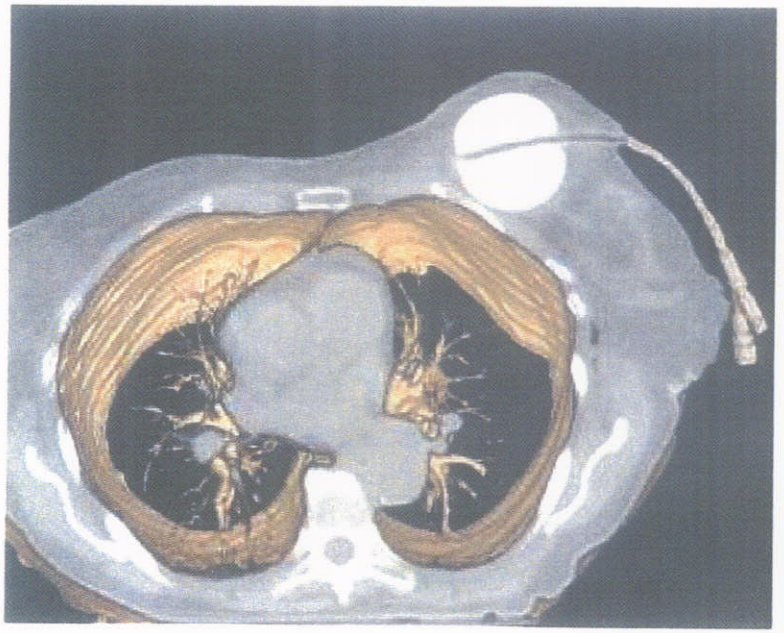
1. CT imaging should be used in conjunction with commercially available treatment planning software to determine the appropriate source lumens, source dwell positions and dwell times for optimized radiation delivery of a prescribed dose to the targeted treatment volume.
2. Verify correct balloon position, volume, skin spacing and conformance using imaging prior to delivery of each fraction of radiation.
3. The SenoRx applicator red-capped, radiation source wire lumens are numbered '1', '2', '3', '4' and '5' and positioned as shown in Figure 3. Lumen number '1' corresponds to the offset lumen closest and parallel to the longitudinal radiopaque line (M) along the outside of the catheter. Lumen number '5' corresponds to the central lumen. Remove the red caps and use commercially available connectors to attach the source lumens to the afterloader. After each treatment replace the red caps.

- REMOVAL

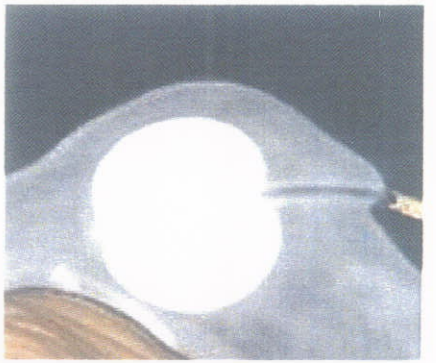
Remove the SenoRx applicator by first attaching a syringe to the Inflation Port and deflating the balloon and then simultaneously rotating and pulling (unscrewing) the catheter from the cavity.

Exhibit G

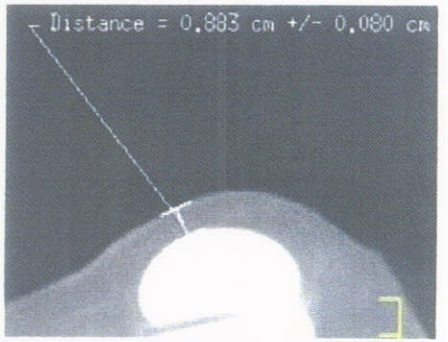
Appropriateness for Treatment



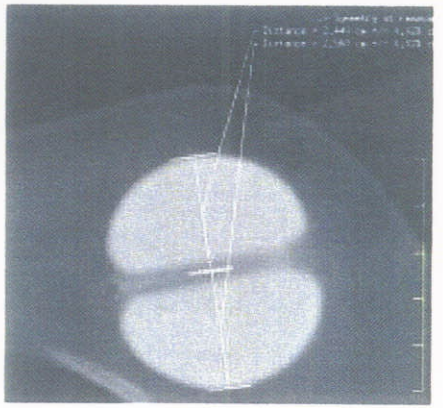
3-Dimensional rendering of applicator surface



Tissue Conformance



Skin Spacing

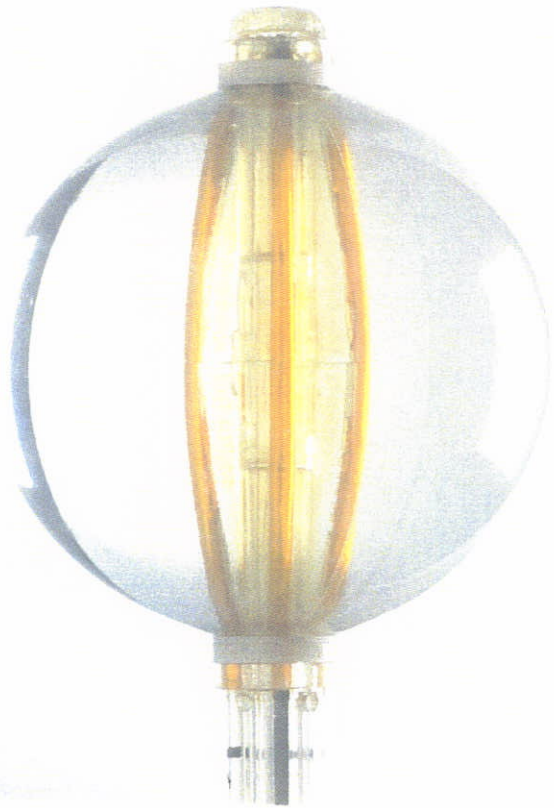


Balloon Diameter & Symmetry

Balloon Brachytherapy Evolves…

- Clinicians specifically asked for the ability to…
  - Reduce skin dose
  - Reduce hot spots
  - Reduce chest wall dose
  - Consider potential for use in smaller breasts
  - Have greater dosimetric control

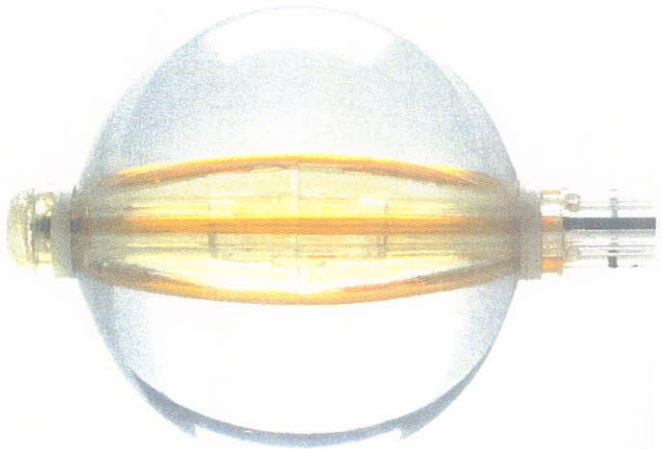
Balloon Brachytherapy Evolves…

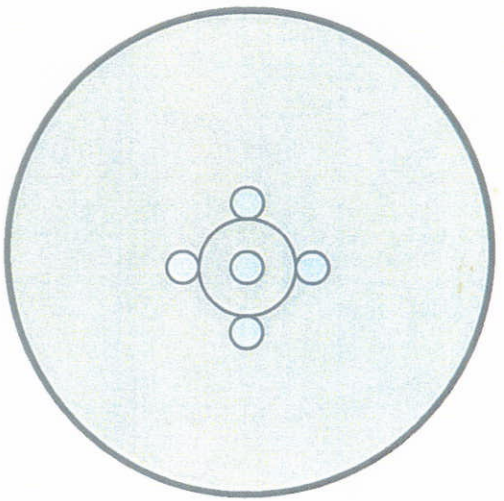


Contura™ MLB

- Brings together the strengths of the balloon
  - Lift tissue away from source
  - Fixates the geometry
- Offers the flexibility of dose control through multiple lumens/dwells

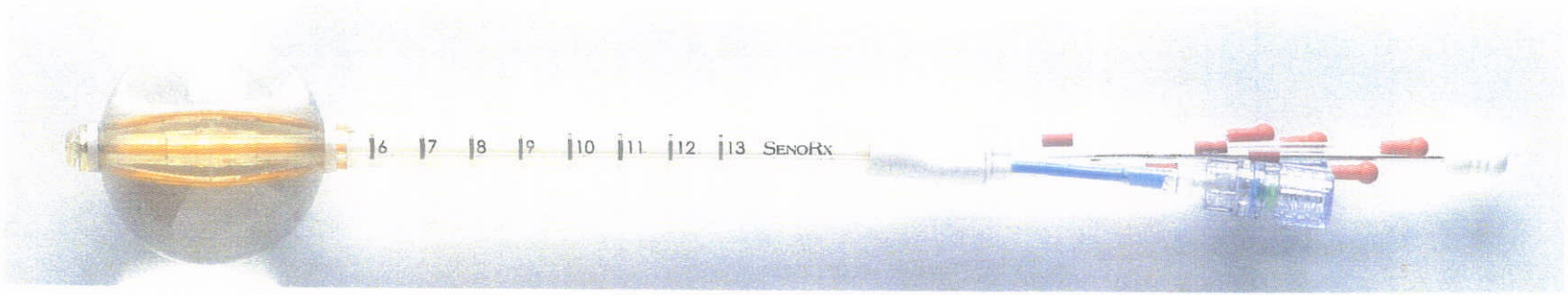
Contura™ MLB





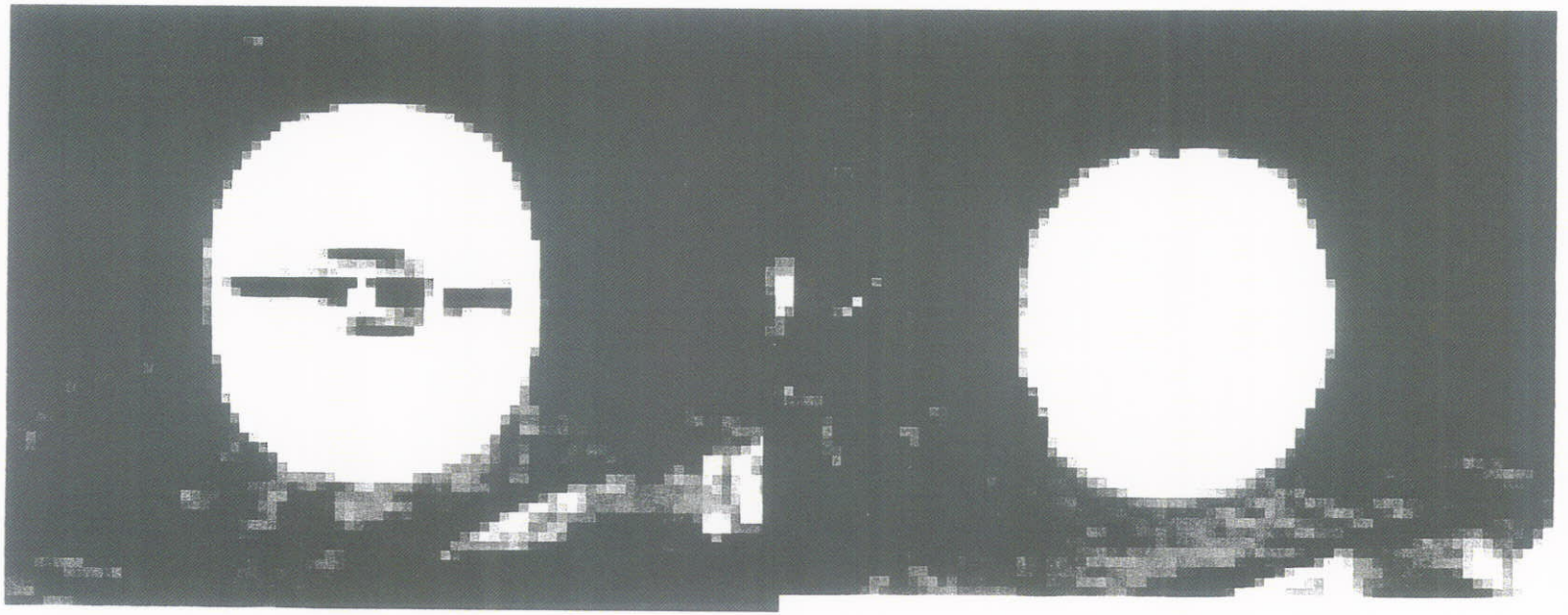
- 5 Tx lumens – 1 central, 4 offset (5mm) from center
- Rigidly fixed into position
- Evacuation ports proximal and distal to balloon

Contura™ MLB



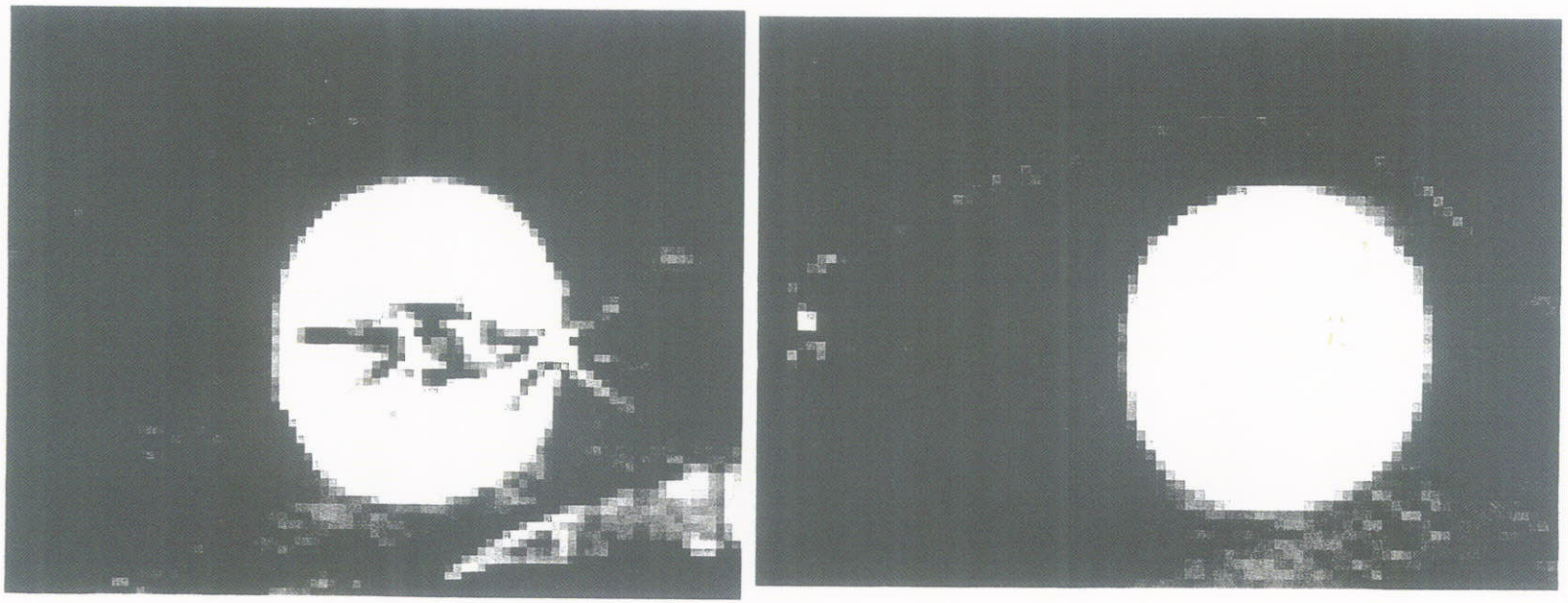
- 4-5cm variable balloon – 33cc to 58cc fill volume
- Shaft diameter – 8 mm, Shaft length – 16cm to hub
- One inflation port
- One vacuum port
- Orientation line on shaft – Catheter #1

Overcoming Tissue to Balloon Conformance Issues



>10% Air/Seroma in PTV at Planning CT requires Mandatory Explantation

Overcoming Tissue to Balloon Conformance Issues



Employ use of Vacuum Lumen to remove air/seroma

- Post Aspiration
- <10% air in PTV

Case Salvaged!

Overcoming Balloon Asymmetry Issues

Deviation of central lumen by 2mm or more requires -

MANDATORY EXPLANTATION

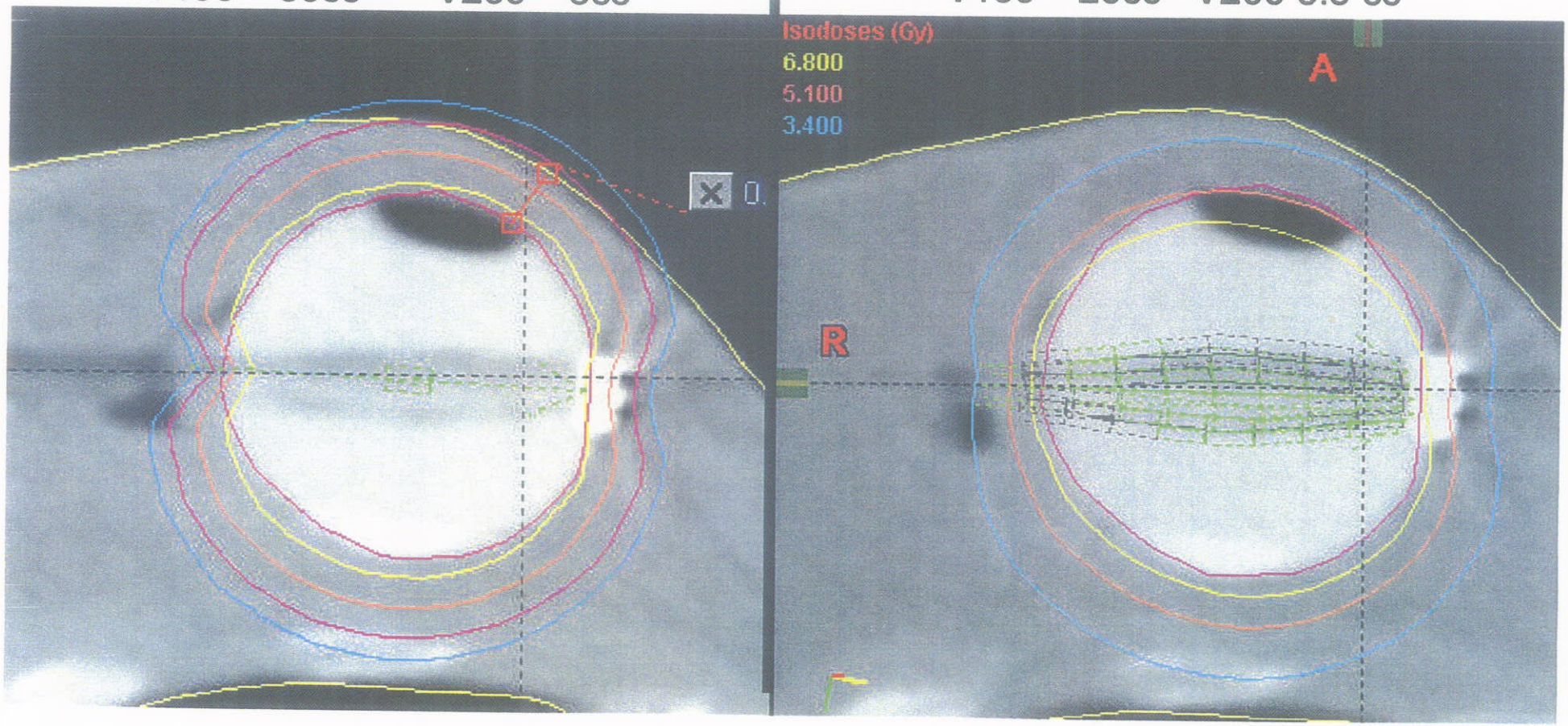
Dosimetric potential

- Skin/Rib dose
  - Every mm counts
  - Skin cosmesis – 4-6 mm critical distance
  - Dose from single dwell, 5cm dia. balloon, 3.4Gy
    - 3mm from balloon surface – 5.8 Gy – 170%
    - 4mm from balloon surface – 5.3 Gy – 157%
    - 5mm from balloon surface – 4.9 Gy – 145%
    - 6mm from balloon surface – 4.6 Gy – 135%
    - 7mm from balloon surface – 4.3 Gy – 128%

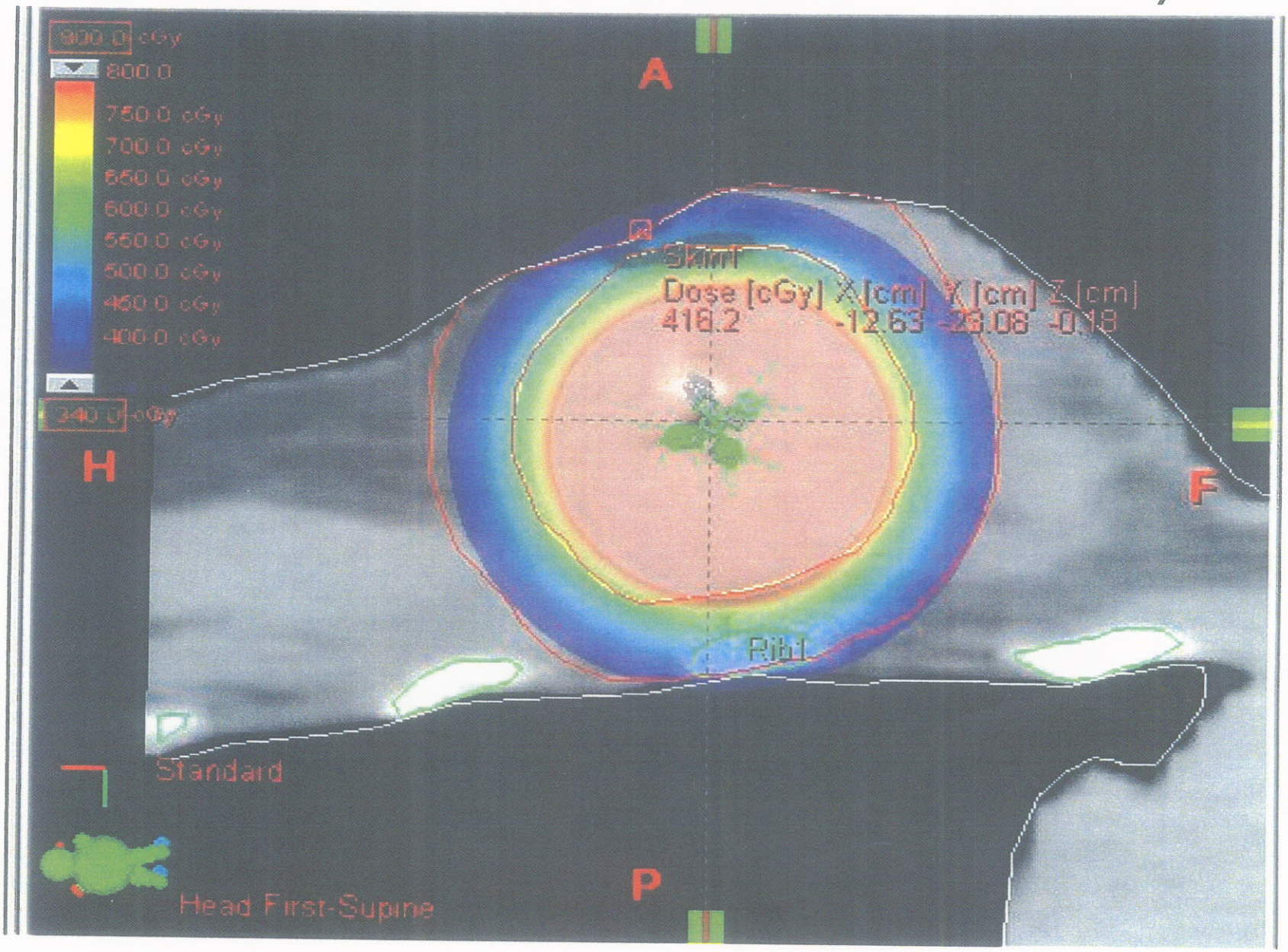
Comparison – Skin spacing 6.5 mm

Single-lumen, Single dwell
Max skin – 4.3 Gy
PTV coverage - >95%/95%
V150 – 30cc V200 – 8cc

Multi-lumen, Multi dwell
Max skin – 2.9 Gy
PTV coverage - >95%/95%
V150 – 20cc V200 3.5 cc



Balloon to Skin Distance = 2mm Skin Dose = 416.2 cGy or 122%



2mm Contura skin distance gets about the same dose as 8mm skin distance (Mammosite)

Dose Volume Histogram

Plan

Senorx1

Treatment %: 100

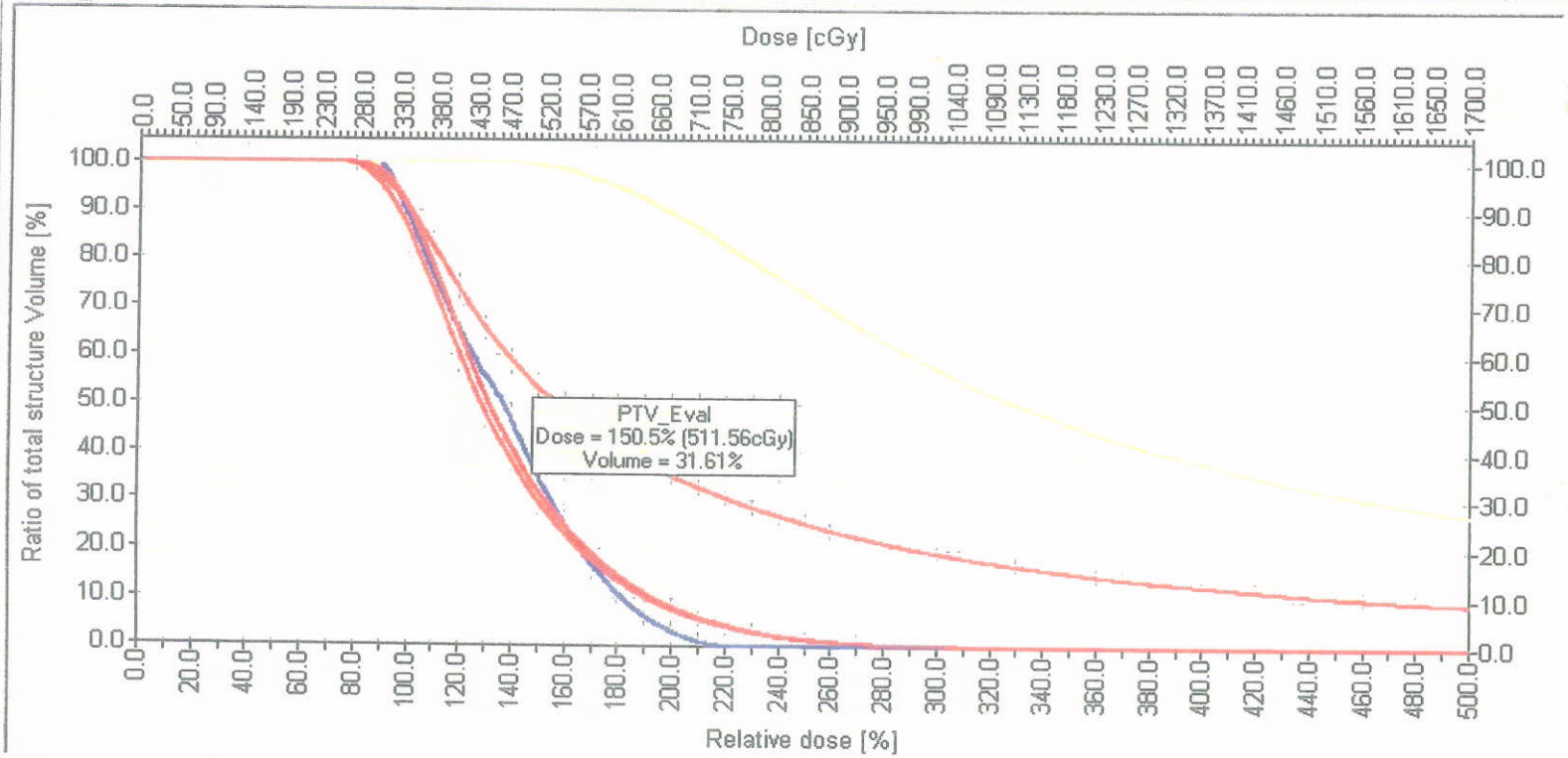
Prescribed dose [cGy]: 340

Structures and Expressions

Structure	Coverage [%] / [%]	Volume [cm³]	Min [%]	Max [%]	Mean [%]	Modal [%]	Median [%]	STD
Air	100.0 / 75.5	0.5	90.1	223.0	138.1	109.8	136.9	30.70
Balloon	100.0 / 99.5	48.0	138.8	11666.8	515.0	243.5	329.9	604.37
Body								
BodyWall								
Bone, NOS								
CTV	100.0 / 100.0	142.6	75.3	11666.8	263.8	113.4	156.6	393.75
PTV	100.0 / 100.2	94.7	75.3	405.9	137.3	113.4	128.3	38.70
PTV_Eval	100.0 / 100.2	88.2	78.2	405.9	140.6	113.4	131.4	38.08
Whole dose matrix								

Add... Edit... Delete Contents:

Histogram



Calculate

Print... Export...

Grid

Type:
- Cumulative
- Differential
- Natural

Volume scale:
- Relative [%]
- Absolute [cm³]

Dose range [%]: 0 to 500

Apply range

Close

V150 still within B39 constraints

Dose Volume Histogram

Plan

Senorx1

Treatment %: 100

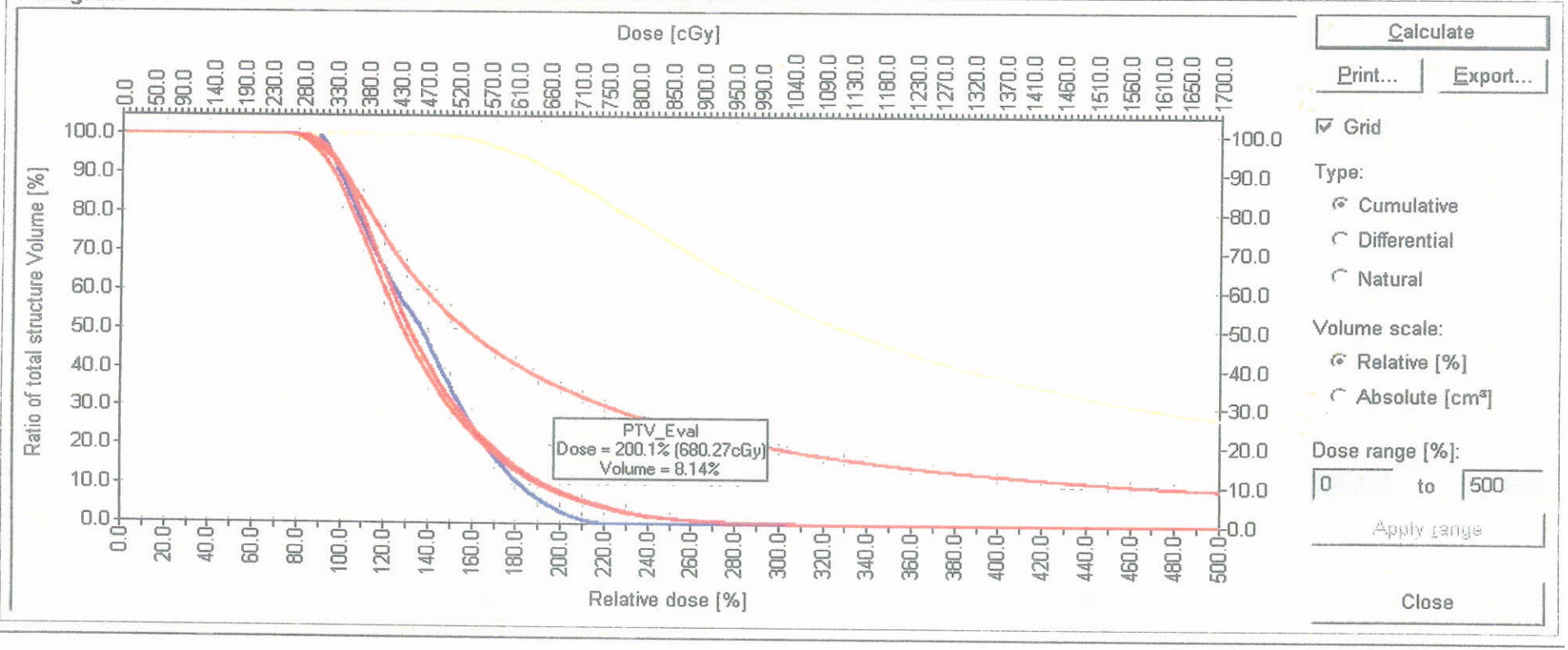
Prescribed dose [cGy]: 340

Structures and Expressions

Structure	Coverage [%] / [%]	Volume [cm³]	Min [%]	Max [%]	Mean [%]	Modal [%]	Median [%]	STD
☑ Air	100.0 / 75.5	0.5	90.1	223.0	138.1	109.8	136.9	30.70
☑ Balloon	100.0 / 99.5	48.0	138.8	11666.8	515.0	243.5	329.9	604.37
☐ Body								
☐ BodyWall								
☐ Bone, NOS								
☑ CTV	100.0 / 100.0	142.6	75.3	11666.8	263.8	113.4	156.6	393.75
☑ PTV	100.0 / 100.2	94.7	75.3	405.9	137.3	113.4	128.3	38.70
☑ PTV_Eval	100.0 / 100.2	88.2	78.2	405.9	140.6	113.4	131.4	38.08
☐ Whole dose matrix								

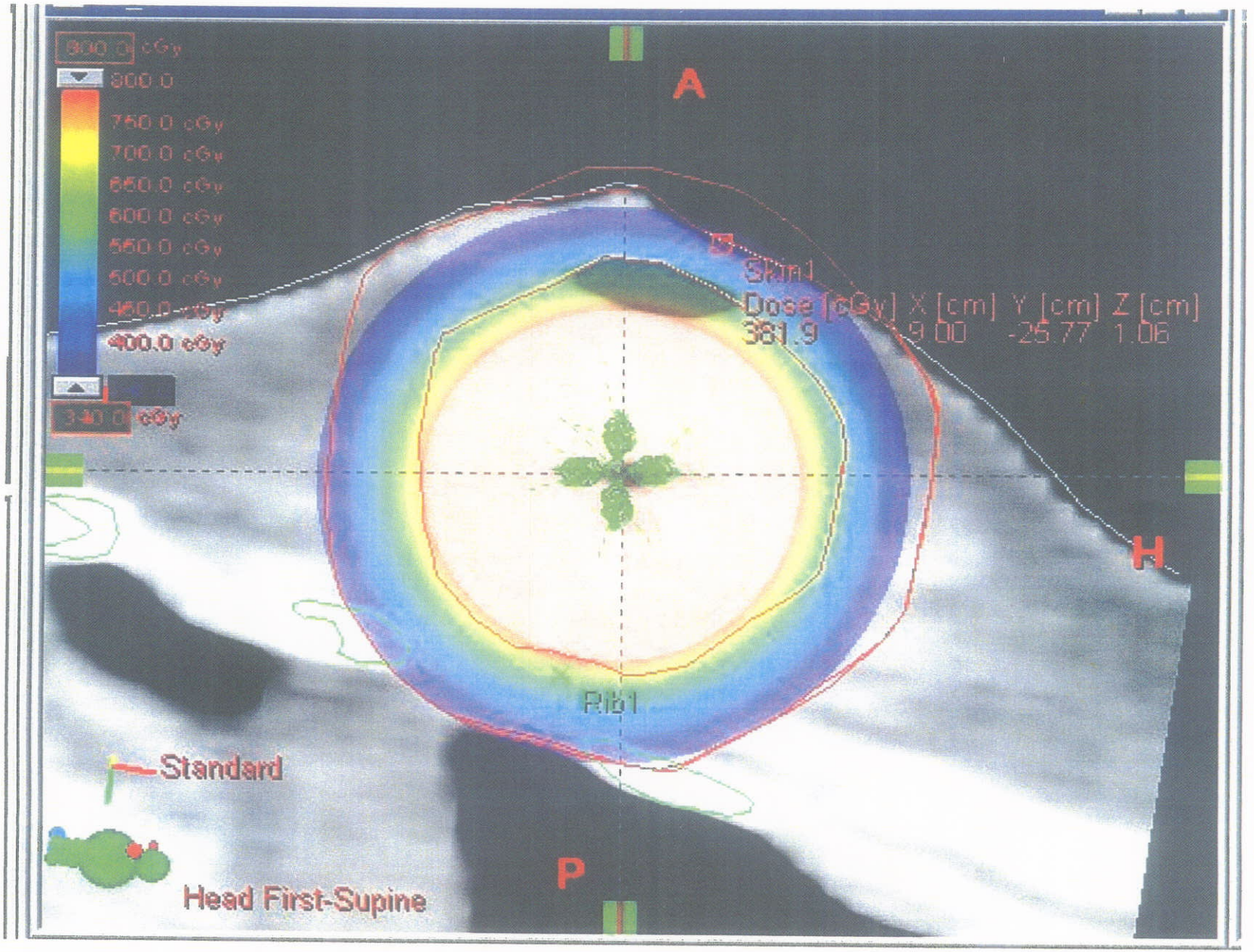
Add... Edit... Delete Contents:

Histogram



V200 within B39

Balloon to Skin Distance = 3mm Skin Dose = 381.9 cGy or 112%



3mm skin bridge: still getting 112% dose: Equivalent to 9mm skin (Mammosite)

se Volume Histogram

Plan

Senorx1

Treatment %: 100

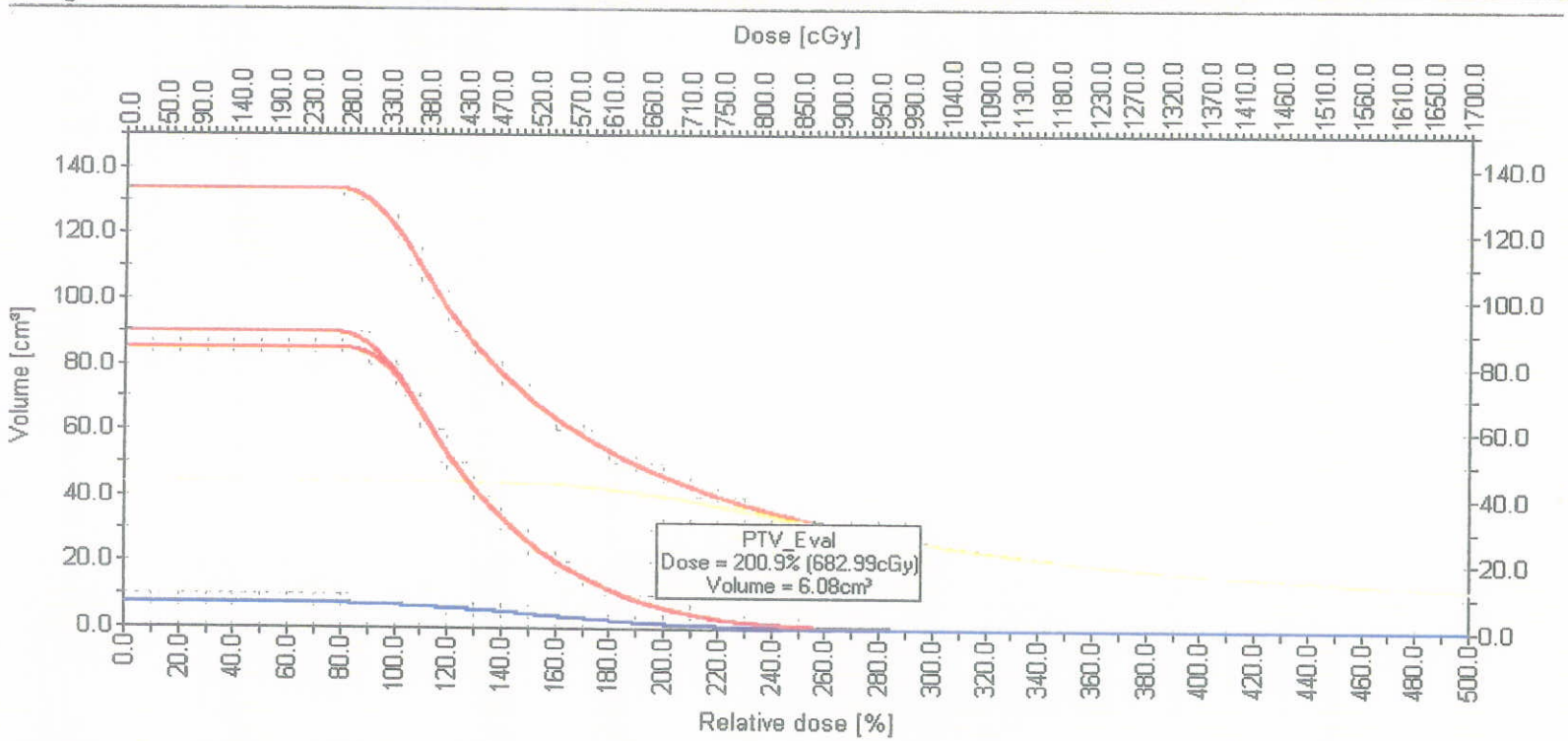
Prescribed dose [cGy]: 340

Structures and Expressions

	Structure	Coverage [%] / [%]	Volume [cm³]	Min [%]	Max [%]	Mean [%]	Modal [%]	Median [%]	STD
	Body								
	Bone, NOS								
	CTV	99.8 / 99.8	134.0	77.0	8239.1	261.7	107.0	154.8	350.83
	PTV	99.6 / 99.8	90.1	77.0	558.3	136.5	107.0	127.4	37.84
	Body_Wall								
	Balloon	100.0 / 99.7	43.9	142.9	8239.1	518.0	274.0	333.6	523.85
	PTV_Eval	100.0 / 100.0	85.2	77.5	558.3	138.6	113.9	129.7	37.29
	Air	100.0 / 98.7	7.2	72.6	284.2	162.3	254.2	159.2	41.74
	Whole dose matrix								

Add... Edit Delete Contents:

Histogram



Calculate

Print... Export...

Grid

Type:
- Cumulative
- Differential
- Natural

Volume scale:
- Relative [%]
- Absolute [cm³]

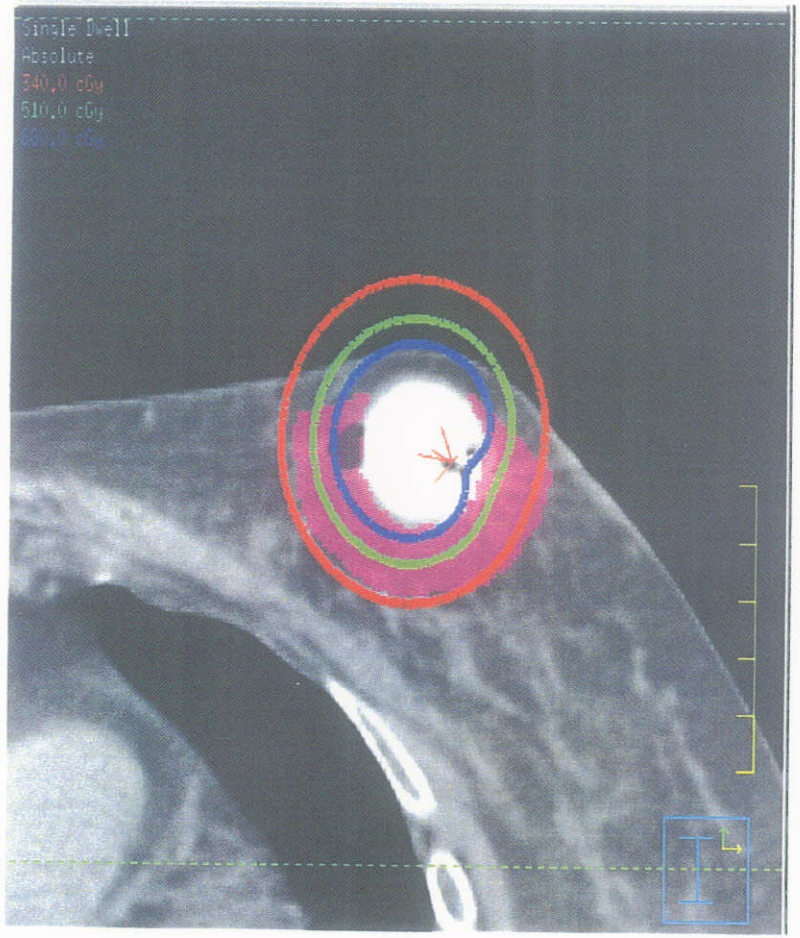
Dose range [%]: 0 to 500

Apply range

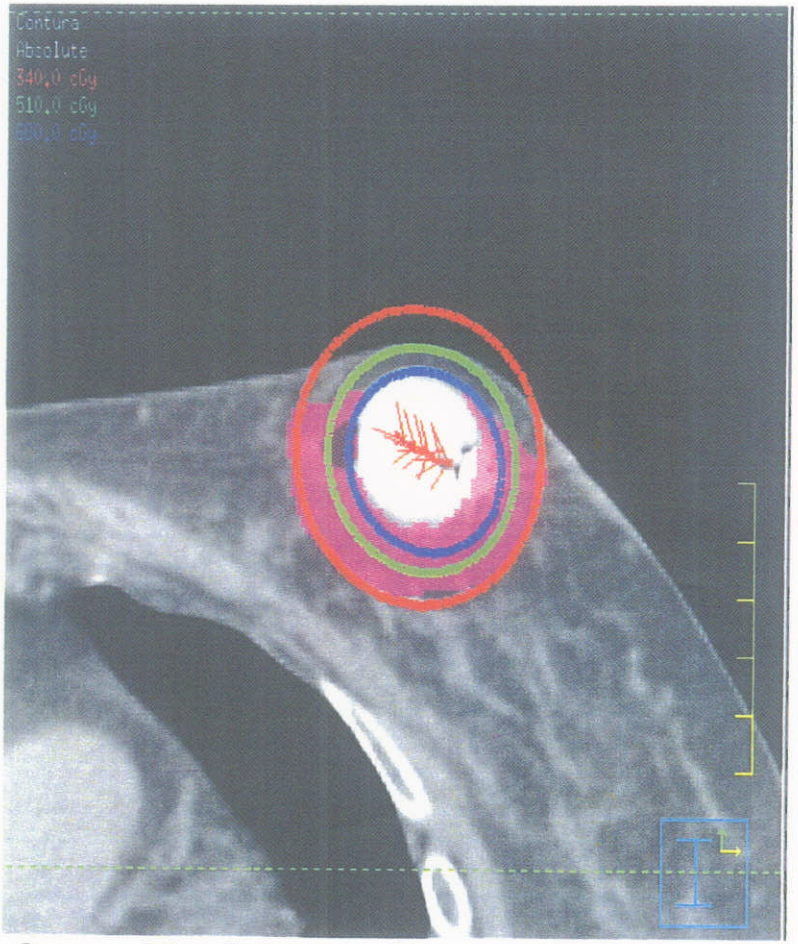
Close

V200: 6cc!

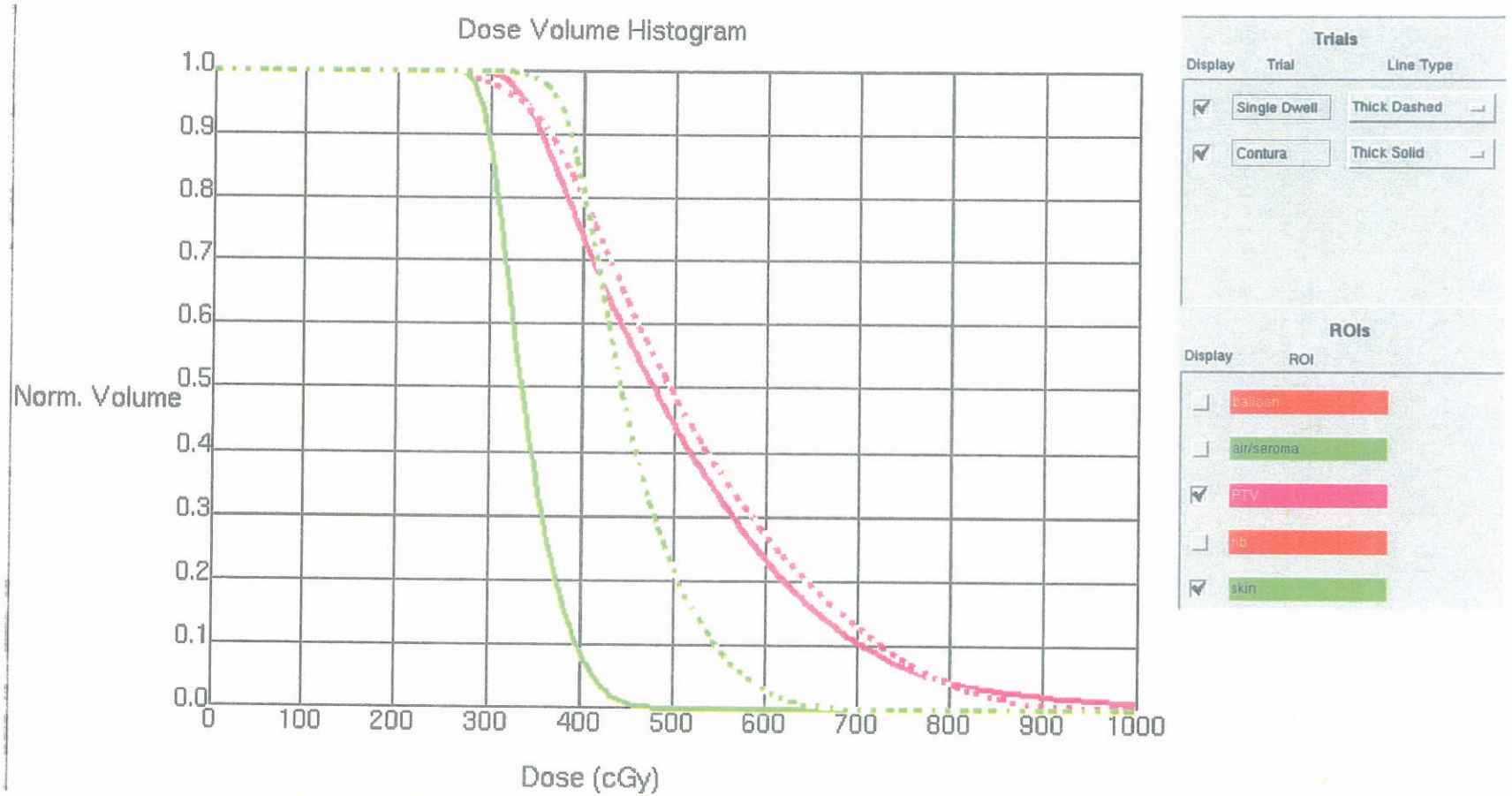
Overcoming Skin Distance Issues



3mm skin distance single dwell central lumen



3mm skin distance Contura multiple dwell, multiple lumens



Minimum balloon to skin distance: ~~3mm~~ 7mm	V100	V150 (cc)	V200 (cc)	Max. skin dose
Single Dwell	94%	25.59	8.42	195%
Contura	94%	23.01	6.81	135%

~ 7mm Single Dwell